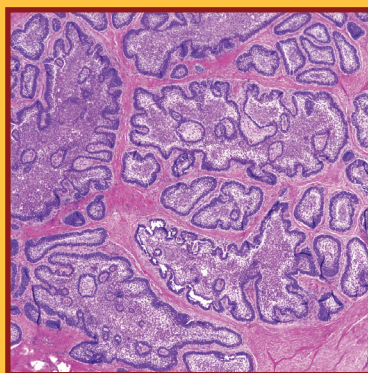
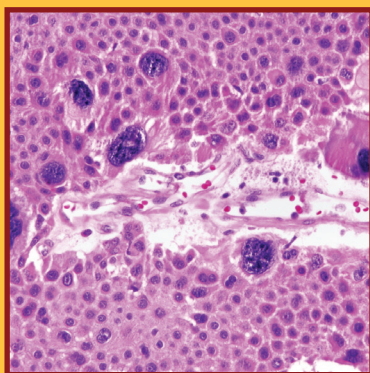
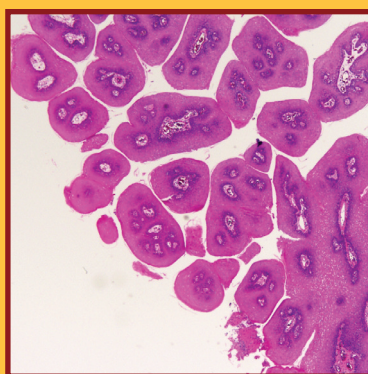
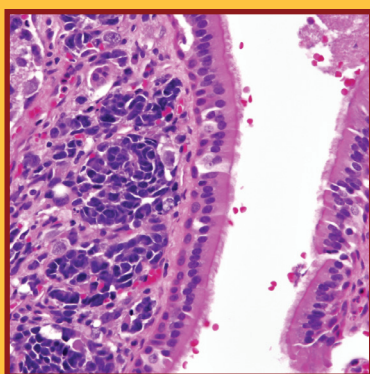


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Demos Surgical  
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# HEAD AND NECK PATHOLOGY



PAUL E. WAKELY JR.



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## **Head and Neck Pathology**



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## Head and Neck Pathology

**PAUL E. WAKELY JR, MD**

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New York

ISBN: 978-1-933864-84-6  
eISBN: 978-1-617050-22-4

*Acquisitions Editor:* Richard Winters  
*Production Editor:* Dana Bigelow  
*Compositor:* S4Carlisle Publishing Services  
*Printer:* Bradford & Bigelow

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#### **Library of Congress Cataloging-in-Publication Data**

Wakely, Paul E.

Head and neck pathology / Paul E. Wakely Jr.  
p.; cm.—(Demos surgical pathology guides)

Includes bibliographical references and index.

ISBN-13: 978-1-933864-84-6 (alk. paper)

ISBN-10: 1-933864-84-2 (alk. paper)

ISBN-13: (invalid) 978-1-61705-022-4 (e-ISBN) 1. Head—Pathophysiology.

2. Neck—Pathophysiology. 3. Head—Diseases—Diagnosis. 4. Neck—Diseases—Diagnosis.

I. Title. II. Series: Demos surgical pathology guides.

[DNLM: 1. Head—pathology. 2. Head—surgery. 3. Neck—pathology.

4. Neck—surgery. WE 705]

RC936.W35 2011

617.5'1—dc23

2011026787

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12 13 14 15 5 4 3 2 1

# Contents

Series Foreword ix  
Preface xi

1. Oral Cavity/Nasopharynx 1

**Nonneoplastic Lesions 2**

        Necrotizing Sialometaplasia 2

        Mucocele/Ranula/Mucus Retention Cyst 4

        Irritation Fibroma 6

**Benign Neoplasms 8**

        Rhabdomyoma, Adult Type 8

        Granular Cell Tumor 10

        Nasopharyngeal Angiofibroma 12

**Malignant Neoplasms 14**

        Epithelial Precancerous Lesions 14

        Squamous Cell Carcinoma, Conventional Type 14

        Nasopharyngeal Carcinoma, Nonkeratinizing Undifferentiated Type 18

        Alveolar Soft Part Sarcoma 20

        Plasmablastic Lymphoma 22

        Kaposi Sarcoma 24

2. Nasal Cavity and Paranasal Sinuses 27

**Nonneoplastic Lesions 28**

        Chronic Nonspecific Sinusitis 28

        Sinonasal Polyps 30

        Allergic Fungal Sinusitis (AFS) 32

        Fungal Sinusitis 34

**Benign Neoplasms 36**

        Schneiderian Papilloma 36

        Lobular Capillary Hemangioma [Pyogenic Granuloma] 38

        Glomangiopericytoma 40

        Solitary Fibrous Tumor 42

**Malignant Neoplasms 44**

        Sinonasal Adenocarcinoma (SNA), Intestinal Type 44

        Olfactory Neuroblastoma (ONB) 46

|                                                    |            |
|----------------------------------------------------|------------|
| Sinonasal Undifferentiated Carcinoma [SNUC]        | 48         |
| Extranodal NK/T-cell Lymphoma, Nasal Type          | 50         |
| Mucosal Malignant Melanoma                         | 52         |
| Rhabdomyosarcoma (RMS)                             | 54         |
| <b>3. Oro/Hypopharynx/Larynx</b>                   | <b>57</b>  |
| <b>Nonneoplastic Lesions</b>                       | <b>58</b>  |
| Contact Ulcer                                      | 58         |
| Vocal Cord Polyp/Nodules                           | 60         |
| Laryngeal Cysts                                    | 62         |
| Hyperplastic Alternations of the Mucosa            | 64         |
| <b>Benign Neoplasms</b>                            | <b>66</b>  |
| Squamous Papilloma                                 | 66         |
| Inflammatory Myofibroblastic Tumor                 | 68         |
| <b>Malignant Neoplasms</b>                         | <b>70</b>  |
| Basaloid Squamous Cell Carcinoma                   | 70         |
| Verrucous Carcinoma                                | 72         |
| Spindle Cell Squamous Carcinoma (Lane Tumor)       | 74         |
| Papillary Squamous Cell Carcinoma                  | 76         |
| Small Cell Neuroendocrine Carcinoma                | 78         |
| Moderately Differentiated Neuroendocrine Carcinoma | 80         |
| Laryngeal Chondrosarcoma                           | 82         |
| <b>4. Salivary Gland</b>                           | <b>85</b>  |
| <b>Nonneoplastic Lesions</b>                       | <b>86</b>  |
| Sialolithiasis                                     | 86         |
| Chronic Fibrosing Sialadenitis (Kuttner Tumor)     | 88         |
| Lymphoepithelial Sialadenitis                      | 90         |
| <b>Benign Neoplasms</b>                            | <b>92</b>  |
| Pleomorphic Adenoma                                | 92         |
| Warthin Tumor                                      | 94         |
| Basal Cell Adenoma                                 | 96         |
| Oncocytoma                                         | 98         |
| Myoepithelioma                                     | 100        |
| <b>Malignant Neoplasms</b>                         | <b>102</b> |
| Mucoepidermoid Carcinoma                           | 102        |
| Acinic Cell Adenocarcinoma (ACC)                   | 104        |
| Adenoid Cystic Carcinoma (AdCC)                    | 106        |
| Polymorphous Low-Grade Adenocarcinoma              | 108        |
| Epithelial-Myoepithelial Carcinoma                 | 110        |
| Clear Cell Carcinoma, NOS                          | 112        |
| Salivary Duct Carcinoma                            | 114        |
| Carcinoma Ex Pleomorphic Adenoma                   | 116        |

|                                                         |     |
|---------------------------------------------------------|-----|
| 5. Gnathic Bones                                        | 119 |
| <b>Nonneoplastic Lesions</b>                            | 120 |
| Fibrous Dysplasia, Craniofacial                         | 120 |
| <b>Benign Neoplasms</b>                                 | 122 |
| Osteoma/Exostosis                                       | 122 |
| Ossifying Fibroma (Cemento-Ossifying Fibroma)           | 124 |
| Ameloblastoma                                           | 126 |
| Ameloblastic Fibroma                                    | 128 |
| Calcifying Epithelial Odontogenic (Pindborg) Tumor      | 130 |
| Keratocystic Odontogenic Tumor (Odontogenic Keratocyst) | 132 |
| Odontogenic Myxoma                                      | 134 |
| Odontoma, Complex Type                                  | 136 |
| <b>Malignant Neoplasms</b>                              | 138 |
| Craniofacial Osteosarcoma, Conventional Type            | 138 |
| 6. Ear                                                  | 141 |
| <b>Nonneoplastic Lesions</b>                            | 142 |
| Keloid                                                  | 142 |
| Chondrodermatitis Nodularis Chronicus Helicis           | 144 |
| Cholesteatoma                                           | 146 |
| Cholesterol Granuloma                                   | 148 |
| <b>Benign Neoplasms</b>                                 | 150 |
| Langerhans Cell Histiocytosis                           | 150 |
| Jugulotympanic Paraganglioma                            | 152 |
| Middle Ear Meningioma                                   | 154 |
| Ceruminous Adenoma                                      | 156 |
| Middle Ear Adenoma                                      | 158 |
| Vestibular Schwannoma (Acoustic Neuroma)                | 160 |
| Endolymphatic Sac Papillary Tumor (Heffner Tumor)       | 162 |
| 7. Soft Tissue/Miscellaneous                            | 165 |
| <b>Nonneoplastic Lesions</b>                            | 166 |
| Branchial Cleft Cyst                                    | 166 |
| Nodular Fasciitis                                       | 168 |
| <b>Benign Neoplasms</b>                                 | 170 |
| Lymphangioma                                            | 170 |
| Teratoma                                                | 172 |
| Fibromatosis                                            | 174 |
| Spindle Cell/Pleomorphic Lipoma                         | 176 |
| References                                              | 179 |
| Index                                                   | 191 |



## Series Foreword

The field of surgical pathology has gained increasing relevance and importance over the years as pathologists have become more and more integrated into the health care team. To the need for precise histopathologic diagnoses has now been added the burden of providing our clinical colleagues with information that will allow them to assess the prognosis of the disease and predict the response to therapy. Pathologists now serve as key consultants in the patient management team and are responsible for providing critical information that will guide their therapy. With the progress gained due to the insights obtained from the application of newer diagnostic techniques, surgical pathology has become progressively more complex. As a result, diagnoses need to be more detailed and specific and the number of data elements required in the generation of a surgical pathology report have increased exponentially, making management of the information required for diagnosis cumbersome and sometimes difficult.

The past 15 years have witnessed an explosion of information in the field of pathology with a massive proliferation of specialized textbooks appearing in print. For the most part, such texts provide in-depth and detailed coverage of the various areas in surgical pathology. The purpose of this series is to bridge the gap between the major subspecialty texts and the large, double-volume general surgical pathology textbooks, by providing compact, single-volume monographs that will succinctly address the most salient and important points required for the diagnosis of the most common conditions. The series is organized following an organ-system format, with single volumes dedicated to individual organs. The volumes are divided on the basis of disease groups, including benign reactive, inflammatory, infectious or systemic conditions, benign neoplastic conditions, and malignant neoplasms. Each chapter consists of a bulleted list of the most pertinent clinical data related to the condition, followed by the most important histopathologic criteria for diagnosis, pertinent use of immunohistochemical stains and other ancillary techniques, and relevant molecular tests when available. This is followed by a section on



differential diagnosis and by a short list of references. Each entity is illustrated with key, high-quality histological images that highlight the most salient and distinctive features that need to be recognized for the correct diagnosis.

These books are intended for the busy practicing pathologist, and for pathology residents and fellows in training who require an easy and simple overview of major diagnostic criteria and key points during the course of routine daily practice. The authors have been carefully chosen for their experience in the field and clarity of exposition in the various topics. It is hoped that this series will fulfill its purpose of providing quick and easy access to critical information for the busy practitioner or trainee, and that it will assist pathologists in their routine practice of the specialty.

*Saul Suster, MD*  
Professor and Chairman  
Department of Pathology  
Medical College of Wisconsin  
Milwaukee, Wisconsin

## Preface

As an anatomic region, the head and neck encompasses a multitude of tissue types. Such diversity leads to a broad array of pathologic alterations, thereby challenging and often humbling the surgical pathologist's interpretive skills. In this era of increasing emphasis on molecular aspects of diagnostic pathology and the rush to apply immunochemistry to almost every entity prior to its histopathologic diagnosis, my intent is to produce a volume that, in a synoptic fashion, concentrates on the salient hematoxylin & eosin (H&E) histopathology of each entity, discussed with brief descriptors of the clinical features, differential diagnosis, and relevant abridged references to each entity.

This is accomplished in a bulleted format with H&E illustrations to match histopathologic criteria. Helpful ancillary tests, in particular, with appropriate immunohistochemical panels are summarized, yet sparingly illustrated. This volume is not all-inclusive; rather, its goal is to produce a synopsis of common as well as a few uncommon entities (but avoiding pathologic curiosities) that are either unique, or most common to the head and neck, and to allow the reader a rapid reference matching critical components of a lesion's histopathology with its clinical aspects and biologic behavior. It focuses on all anatomic areas of this region with the exceptions of cutaneous and endocrine pathology.

All errors of omission or commission are those of the author's, for which I apologize in advance. I am grateful to the series editor for his invitation to produce this volume in conjunction with others in the series, to the Otolaryngology Department at The Ohio State University for a wonderful collegial atmosphere, and to Mr. Rich Winters, Demos Publishing, for his guidance in the production of this volume.

*Paul E. Wakely Jr, MD*



## Oral Cavity/Nasopharynx

### **NONNEOPLASTIC LESIONS**

NECROTIZING SIALOMETAPLASIA

MUCOCELE/RANULA/MUCUS RETENTION CYST

IRRITATION FIBROMA

### **BENIGN NEOPLASMS**

RHABDOMYOMA, ADULT TYPE

GRANULAR CELL TUMOR

NASOPHARYNGEAL ANGIOFIBROMA

### **MALIGNANT NEOPLASMS**

EPITHELIAL PRECANCEROUS LESIONS

SQUAMOUS CELL CARCINOMA, CONVENTIONAL TYPE

NASOPHARYNGEAL CARCINOMA, NONKERATINIZING  
UNDIFFERENTIATED TYPE

ALVEOLAR SOFT PART SARCOMA

PLASMABLASTIC LYMPHOMA

KAPOSI SARCOMA

### Necrotizing Sialometaplasia

#### DEFINITION:

Benign ulcerative, reactive lesion, possibly ischemic in origin; primarily involving minor salivary glands that clinically and histologically mimic squamous carcinoma.

#### CLINICAL FEATURES:

- Painless crater-like ulcer or nodule of palate, oral pain, dysphagia
- Minor salivary glands of the palate are most common site; major salivary glands less often involved and usually occur after radiation therapy

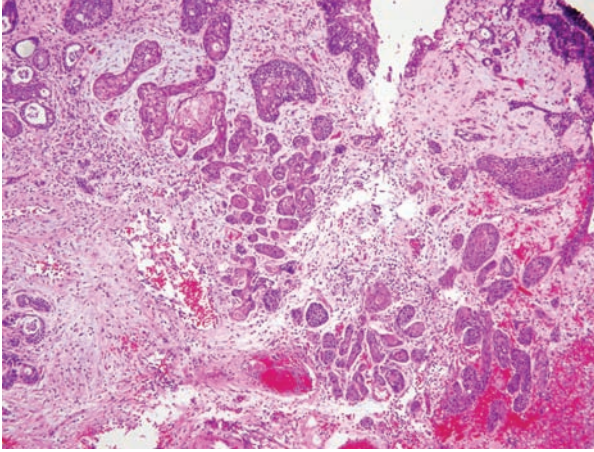
#### GROSS AND HISTOLOGIC FINDINGS:

- Necrosis of seromucinous glands with preservation of the salivary gland lobule
- Squamous metaplasia replaces much of the normal gland acini with preservation of glandular contour (**Figure 1-1**)
- Presence of granulation tissue, inflammation, mucin extravasation in stroma, and pseudoepitheliomatous hyperplasia of overlying mucosa

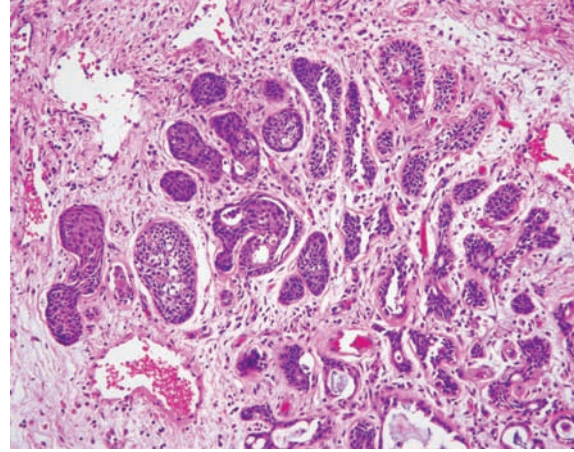
#### DIFFERENTIAL DIAGNOSIS:

- Squamous carcinoma
- Mucoepidermoid carcinoma

## Necrotizing Sialometaplasia



A



B

**FIGURE 1-1** *Necrotizing Sialometaplasia*

**A.** Metaplastic squamous epithelium, having replaced much of the minor salivary gland mucosa, mimics an invasive squamous carcinoma. The mucosal surface is at *top right*.

**B.** This minor salivary gland retains its normal rounded contour, and the metaplastic epithelium lacks cytologic atypia.

### Mucocele/Ranula/Mucus Retention Cyst

#### DEFINITION:

Extravasation of mucus into the surrounding soft tissue creating a pseudocyst secondary to rupture of a salivary gland duct. Ranula is a mucocele that arises in the floor of the mouth, creating a smooth contoured cyst. A mucus retention cyst is a true cyst lined by epithelium, typically of the simple flattened or cuboidal type. Some authorities do not make this distinction and consider them all mucoceles.

#### CLINICAL FEATURES:

- Dome-shaped mucosal nodule/swelling varying from 1–2 mm to 3 cm and most common on the lower lip
- Sometimes translucent
- Broad age range; more common in children and adolescents

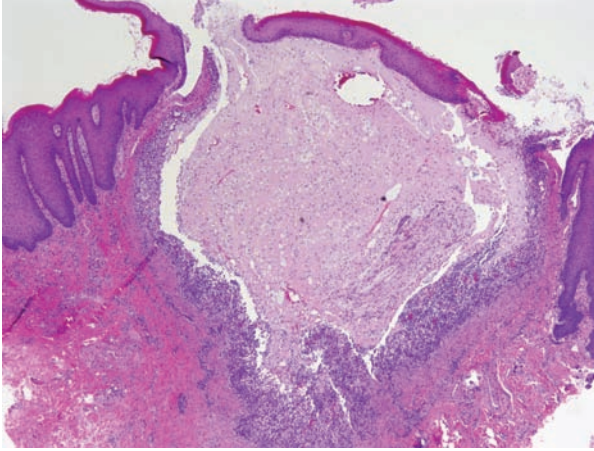
#### GROSS AND HISTOLOGIC FINDINGS:

- No specific gross features
- Irregular dissection of mucus into soft tissue without an epithelial lining
- Numerous foamy macrophages (muciphages) and a varying number of lymphocytes, eosinophils, and plasma cells and occasionally surrounding granulation tissue (**Figure 1-2**)

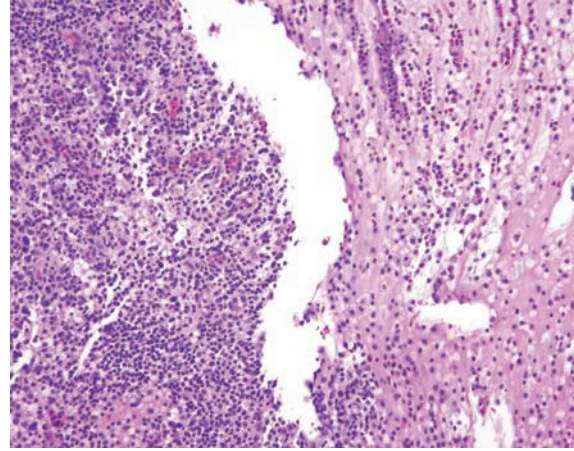
#### DIFFERENTIAL DIAGNOSIS:

- Low-grade mucoepidermoid carcinoma

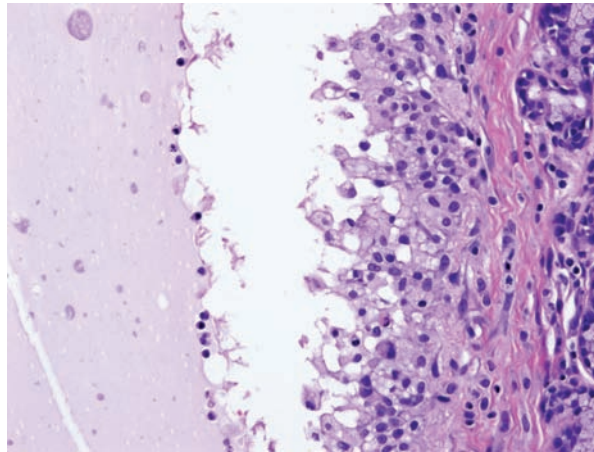
## Mucocele/Ranula/Mucus Retention Cyst



A



B



C

**FIGURE 1-2** *Mucocele/Mucus Cyst*

**A.** Rim of histiocytes and inflammatory cells surrounds this large pool of extravasated mucin. **B.** This mucinous pool (*right*) is filled with foamy histiocytes and inflammatory cells, while the surrounding tissue (*left*) lacks an epithelial lining. **C.** Foamy macrophages are seen at the periphery of this mucocele without a heavy inflammatory component.



### Irritation Fibroma

#### DEFINITION:

Localized submucosal proliferation of fibroblasts and fibrous connective tissue. Thought to be reactive/nonneoplastic, and as such often termed “irritation” fibroma.

#### CLINICAL FEATURES:

- Most occur along the “bite line”: lateral tongue and buccal mucosa; also lip and gingiva
- Women affected twice as often as men; decades 4 to 6
- Typically asymptomatic

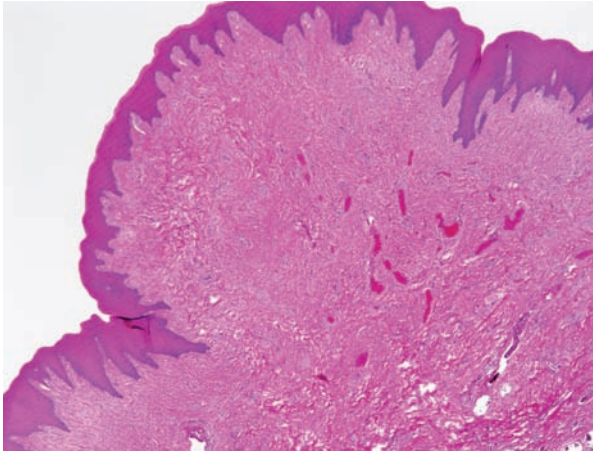
#### GROSS AND HISTOLOGIC FINDINGS:

- Gross: smooth nodule ranging from 0.2 to 2.0 cm similar in color to surrounding mucosa
- Well-circumscribed nodule mass of collagen lacking a capsule and relatively hypocellular (**Figure 1-3**)
- Spindle-shaped fibroblasts are inconspicuous and scant
- Squamous mucosa ranges from normal to thinned to hyperkeratotic

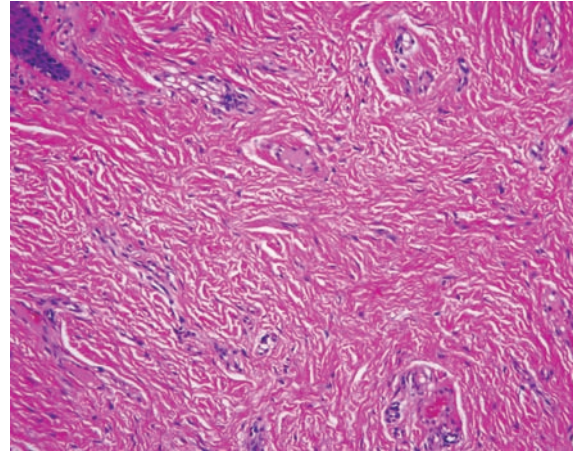
#### DIFFERENTIAL DIAGNOSIS:

- Schwannoma
- Giant cell fibroma
- Granular cell tumor

## Irritation Fibroma



A



B

**FIGURE 1-3** *Irritation Fibroma*

**A.** Collarette of squamous mucosa partially envelops this nodule of fibrous tissue.

**B.** Hypocellular dense fibrous tissue contains cytologically bland fibroblasts.

### Rhabdomyoma, Adult Type

#### DEFINITION:

Benign neoplasm showing skeletal muscle differentiation and capable of local recurrence.

#### CLINICAL FEATURES:

- Mean age, 50 years, male predominance as much as 4:1
- Predilection for supraglottic larynx, oropharynx, and floor of mouth
- May grow to several centimeters
- Nonspecific symptoms include dysphagia, feeling of a “mass” in the mouth, dysphonia

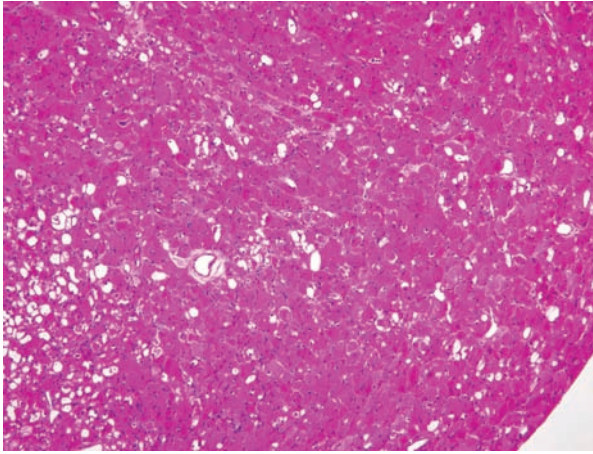
#### GROSS AND HISTOLOGIC FINDINGS:

- Gross: coarsely bosselated, brick-red resembling renal cortex
- Large polygonal cells in solid sheets and nests having a voluminous amount of deeply eosinophilic cytoplasm with cross-striations separated at regular and irregular intervals (**Figure 1-4**)
- “Spider cells” formed by thin strands of cytoplasm separating peripherally placed large PAS-positive glycogen-filled vacuoles
- Cytoplasmic crystalline structures arranged in haphazard fashion (“jackstraw crystals”) formed by hypertrophied Z-bands
- Rounded nuclei, often vesicular with single visible nucleolus; mitoses rare to absent
- Positive IHC: HHF-35 actin, desmin, myogenin, MyoD1, and myoglobin
- PTAH stain highlights crystals and cross-striations

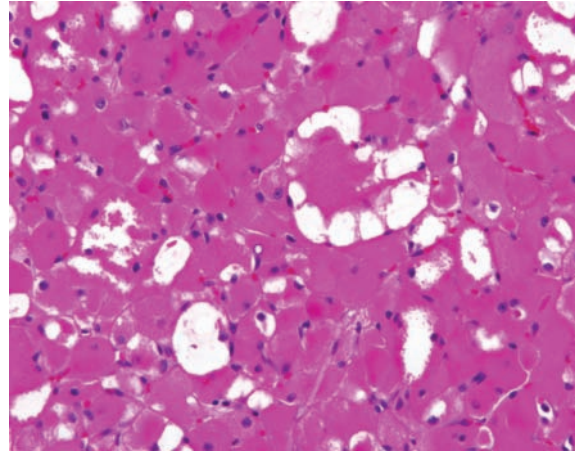
#### DIFFERENTIAL DIAGNOSIS:

- Alveolar soft part sarcoma
- Granular cell tumor
- Crystal-storing histiocytosis
- Oncocytoma

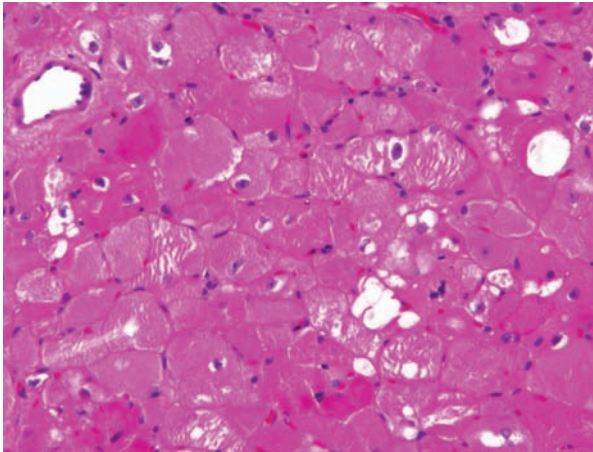
## Rhabdomyoma, Adult Type



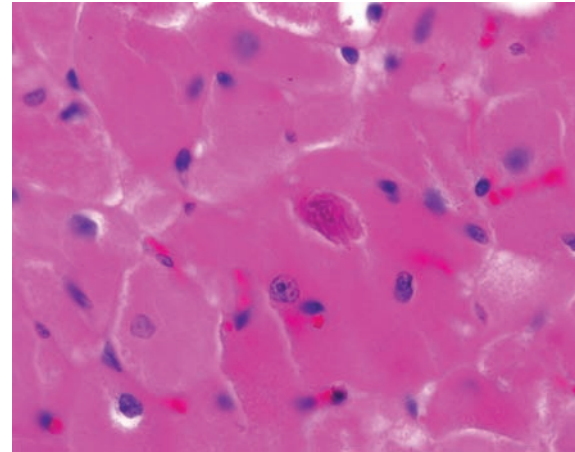
A



B



C



D

**FIGURE 1-4** *Rhabdomyoma, Adult Type*

**A.** Solid sheet of large acidophilic cells contains foci of cytoplasmic vacuolization.

**B.** "Spider" cell contains peripherally placed glycogen-filled vacuoles. **C.** Coarse cross-striations are seen in several cells. **D.** An irregularly shaped "jackstraw" crystal.

### Granular Cell Tumor

#### DEFINITION:

Benign neoplasm with schwannian differentiation and composed of large cells containing numerous lysosomes that confer a coarse granularity to cell cytoplasm.

#### CLINICAL FEATURES:

- Broad age range; mean = decades 4 to 5; <5% locally recur
- Sites include tongue, oropharyngeal mucosa, larynx
- Nonspecific symptoms: dysphagia, dysphonia, chronic cough
- Congenital epulis variant: almost exclusive to the alveolar ridge near the midline of newborns; females affected much more than males

#### GROSS AND HISTOLOGIC FINDINGS:

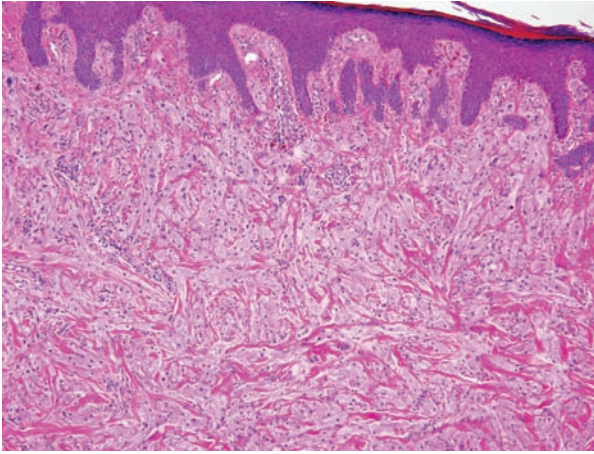
- Gross: dome-shaped nodule, sessile; may be multiple
- Poorly circumscribed proliferation of monomorphic, polygonal cells arranged in sheets, nests, and, less often, trabeculae
- Cells have rounded nuclei, single small discernible nucleoli, and abundant coarsely granular cytoplasm with indistinct cell borders (**Figure 1-5**)
- Mitotic figures rare and necrosis is absent
- Often associated with pseudoepitheliomatous hyperplasia of overlying mucosa
- Positive IHC: S-100, vimentin, and CD68; negative for cytokeratin, actin, myoglobin, desmin, and HMB-45
- Congenital epulis variant: identical histopathology but S-100 negative; lacks mucosal pseudoepitheliomatous hyperplasia

#### DIFFERENTIAL DIAGNOSIS:

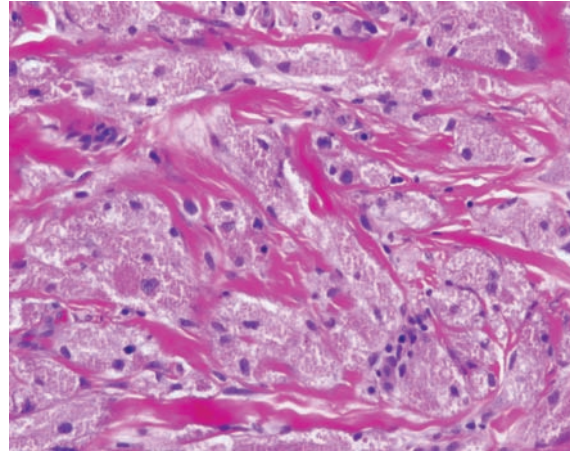
- Alveolar soft part sarcoma
- Paraganglioma
- Well-differentiated squamous carcinoma



## Granular Cell Tumor



A



B

**FIGURE 1-5** *Granular Cell Tumor*

**A.** Large granular cells are immediately subjacent to the oral mucosa, which shows a slight degree of pseudoepitheliomatous hyperplasia. **B.** Thick collagen fibers separate cells with coarse granular cytoplasm.

### Nasopharyngeal Angiofibroma

#### DEFINITION:

Benign fibrous and vascular mesenchymal neoplasm originating in the nasopharynx, and almost exclusive to adolescent and young adult males.

#### CLINICAL FEATURES:

- Median age 15 years, males
- Slow growing, but destructive; large tumors may erode into the skull base
- Nasal obstruction, epistaxis
- Radiologic study reveals a rich vascular supply helping to distinguish it from a sinonasal polyp

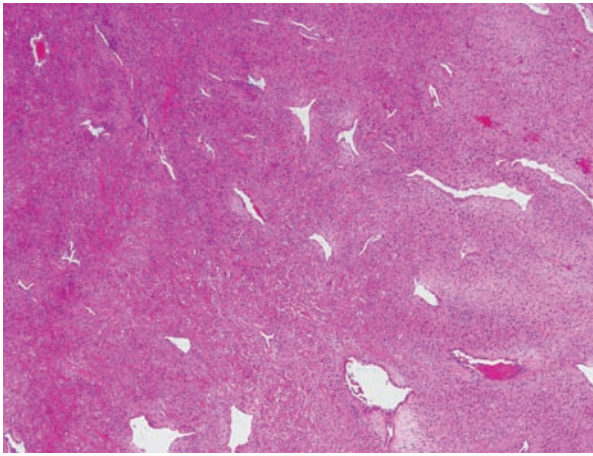
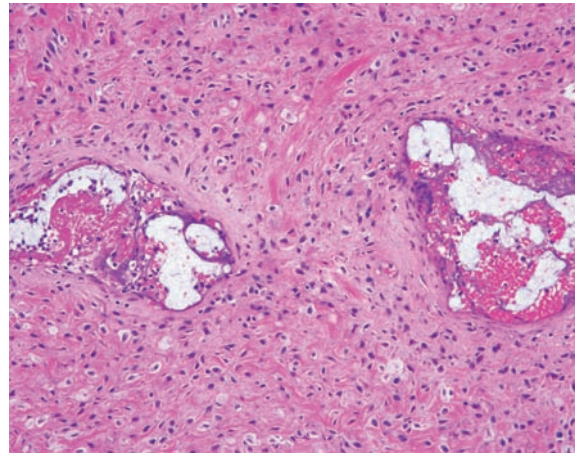
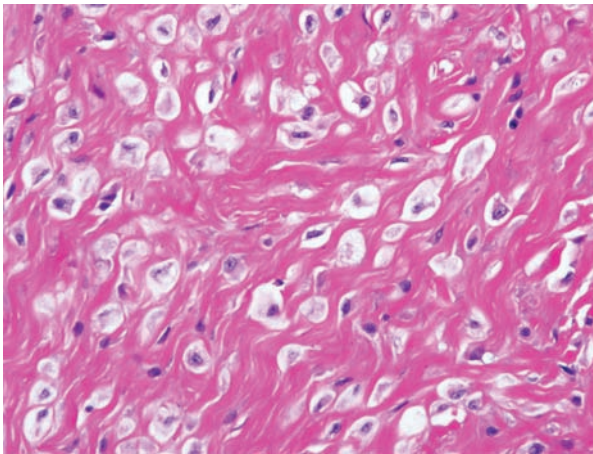
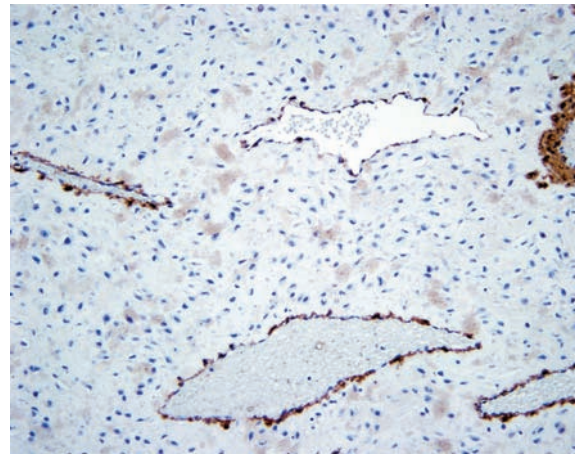
#### GROSS AND HISTOLOGIC FINDINGS:

- Gross: smooth-surfaced polypoid mass with spongy cut surface
- Loose proliferation of stellate, spindle cells in a variably fibrous stroma
- Numerous randomly arranged, ectatic branching vessels range from those with a single layer of endothelium without a muscular coat in small capillaries to larger vessels with pad-like or partially circumferential smooth muscular coats; no elastic lamina (**Figure 1-6**)
- Foreign material may be present secondary to angiographically directed embolization
- Positive IHC: vimentin, CD117,  $\beta$ -catenin, androgen receptor

#### DIFFERENTIAL DIAGNOSIS:

- Sinonasal leiomyoma
- Fibroma
- Solitary fibrous tumor

## Nasopharyngeal Angiofibroma

**A****B****C****D**

**FIGURE 1-6** *Nasopharyngeal Angiofibroma*

**A.** Ectatic branching vessels are set in a fibrous stroma. **B.** Prosthetic material was used to embolize these two vessels. **C.** Some of the polygonal cells in this collagenized stroma have ganglion-like features. **D.** Smooth muscle actin stain shows a complete absence of a smooth muscle wall surrounding many of these vessels.



## Epithelial Precancerous Lesions

### DEFINITION:

Alteration of the surface epithelium consisting of architectural and cytologic changes that are associated with an increased susceptibility to evolve into squamous carcinoma.

### CLINICAL FEATURES:

- Areas of white plaques that cannot be rubbed off (leukoplakia) and/or erythematous, velvety patches (erythroplakia) or a mixture of these
- Some patients complain of a burning sensation or pain depending on the extent of the lesion, but most are asymptomatic
- Most patients are in decades 5 to 6
- M>F: 3–4:1
- Strong association with prolonged tobacco and alcohol use
- Common sites: anywhere in the oral cavity, larynx, and oropharynx

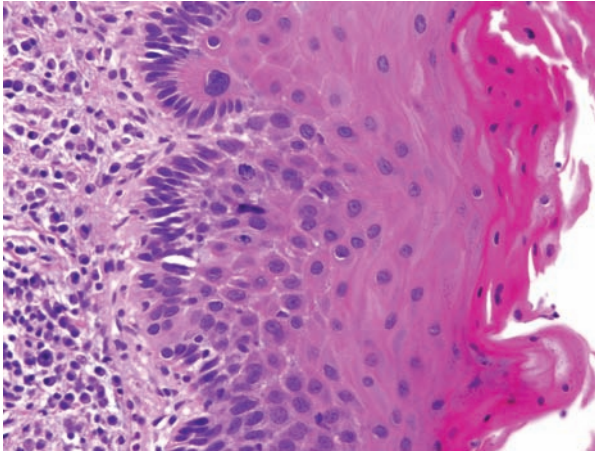
### GROSS AND HISTOLOGIC FINDINGS:

- Gross: leukoplakic foci have sharp, well-demarcated, but irregular borders, and have a warty, or a flat thickened appearance; mixed erythroplakic/leukoplakic areas have a speckled appearance
- Precursor lesions are subdivided into three or four groups depending on the classification used. Most recent WHO classification uses the term *dysplasia* with a scale of 1 (mild dysplasia), 2 (moderate dysplasia), and 3 (severe dysplasia/carcinoma in situ). Other classifications use the same format with different terms. All levels of dysplasia are contained within the surface epithelium with an intact basement membrane.
- Mild (lower third), moderate (lower and middle third), and severe dysplasia (full thickness) relates to the proportion of epithelium that displays these architectural and cytologic abnormalities. Full-thickness dysplasia is not necessary prior to the development of invasive carcinoma. Many authors including the current author subdivide these lesions into only two grades: low- and high-grade dysplasia because of overlapping morphology (**Figure 1-7**).
- Architectural changes include increased cellularity of basal/parabasal cells, loss of polarity, increased mitoses
- Cytologic changes include enlargement in nuclear size and variation in shape, increased nuclear/cytoplasmic (N/C) ratio, increased nuclear chromasia, macronucleoli

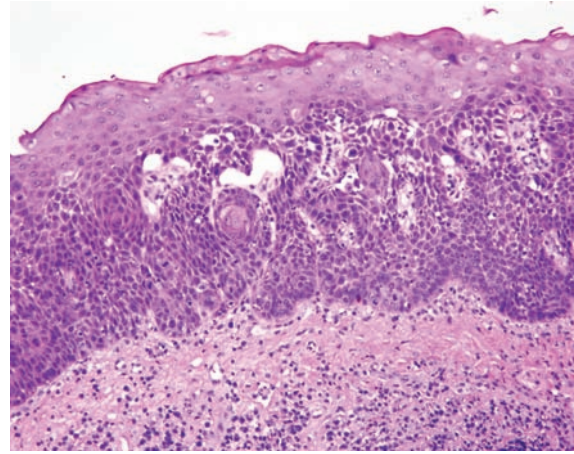
### DIFFERENTIAL DIAGNOSIS:

- Squamous hyperplasia
- Reactive atypia
- Pseudoepitheliomatous hyperplasia

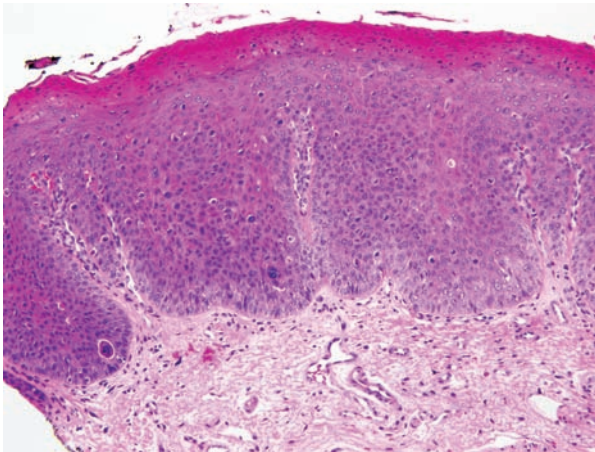
## Epithelial Precancerous Lesions



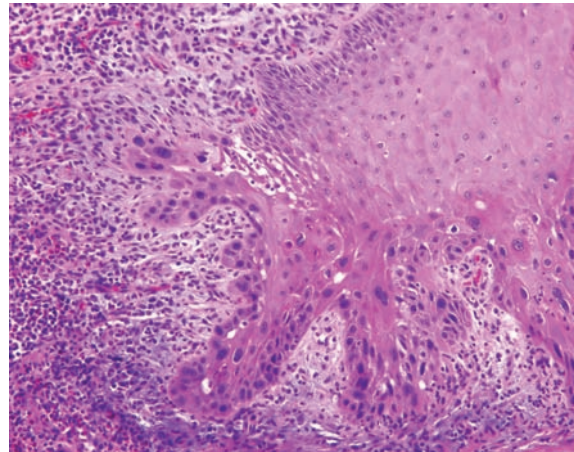
A



B



C



D

**FIGURE 1-7** *Epithelial Precancerous Lesions*

**A. Mild Dysplasia.** The basilar layer shows rare cytomegaly, hyperchromasia, and minimal apoptosis. **B. Moderate Dysplasia.** Hypercellularity and cell disorganization occupy the lower two-thirds of this mucosa. Some pathologists will call this high-grade dysplasia. **C. Carcinoma In Situ/Severe Dysplasia.** Full-thickness hypercellularity, dyskeratotic cells, mitoses at all levels qualify as carcinoma in situ. **D. Early Invasive Squamous Carcinoma.** Benign appearing mucosa shows an abrupt, sharp transformation to squamous carcinoma with downward penetration of malignant cells having markedly enlarged and hyperchromatic nuclei.

### Squamous Cell Carcinoma, Conventional Type

#### DEFINITION:

Invasive malignant epithelial neoplasm with varying degrees of squamous differentiation. The various histologic subtypes are discussed in the larynx section.

#### CLINICAL FEATURES:

- Most patients are decades 5 to 6; rare in children or young adults
- M>F: 3–4:1
- Signs and symptoms include bleeding from the mass, loosening of teeth, pain, halitosis, dysphagia, difficulty with chewing, neck swelling
- Some patients have palpable cervical adenopathy at presentation
- Sites of involvement are similar to those listed for precancerous lesions
- Strong association with prolonged tobacco and alcohol use

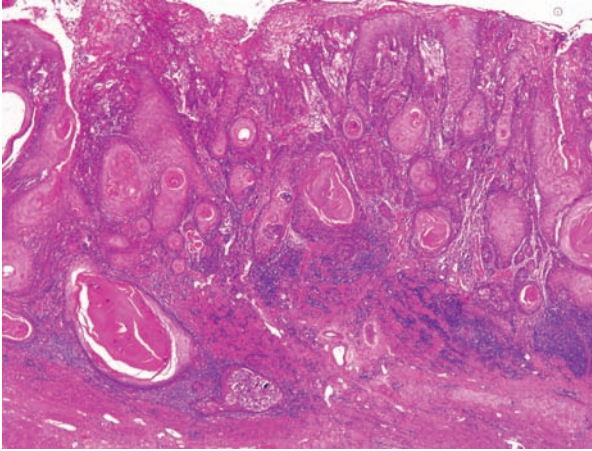
#### GROSS AND HISTOLOGIC FINDINGS:

- Gross: varies from an exophytic, irregularly contoured mass to an endophytic, ulcerated lesion or a flattened plaque-like thickening
- Jagged nests and strands of malignant cells exhibit varying degrees of squamous differentiation. These extend beyond the epithelial basement membrane and show an infiltrative pattern into the submucosa, soft tissues, and even bone. Better differentiated carcinoma displays intercellular bridges between cells, low N/C ratio, cytoplasmic keratinization, and extracellular keratin “pearl” formation, while less-differentiated examples show a lack or almost complete absence of these features (**Figure 1-8**)
- Malignant cells show nuclear enlargement with chromatin clearing, enlarged nucleoli, and irregularities in nuclear contour
- Perineural and vascular space invasion possible
- Increased typical and abnormal mitotic figures
- Coagulation necrosis and increased stromal desmoplasia
- Positive IHC: pan-cytokeratin antibodies

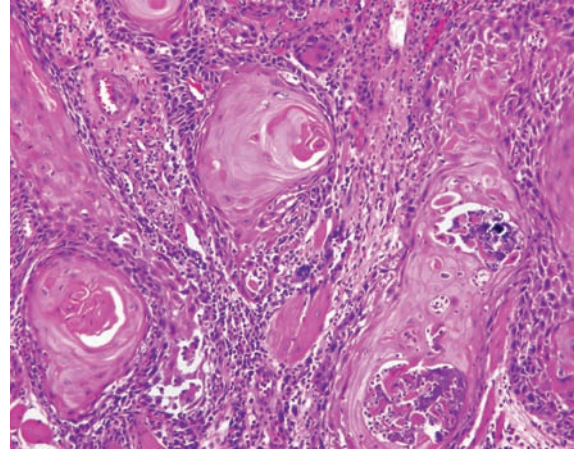
#### DIFFERENTIAL DIAGNOSIS:

- Pseudoepitheliomatous hyperplasia

## Squamous Cell Carcinoma, Conventional Type



A



B

**FIGURE 1-8** *Squamous Cell Carcinoma, Conventional Type*

**A.** Numerous keratinized nests of malignant squamous cells display a “drop-off” quality in their downward migration to the stroma. **B.** In this well-differentiated squamous carcinoma, keratin pearl formation is common.



### Nasopharyngeal Carcinoma, Nonkeratinizing Undifferentiated Type

#### DEFINITION:

Carcinoma composed of undifferentiated large epithelial cells that show evidence of squamous differentiation only at the ultrastructural level. Archaic term: lymphoepithelioma.

#### CLINICAL FEATURES:

- Broad age range, mostly middle-aged men, predilection for Asian population
- Nasal obstruction, epistaxis
- May present initially with cervical lymphadenopathy
- Lateral wall of nasopharynx is most common site, but can also arise in the oropharynx, larynx, hypopharynx, salivary gland, and sites outside the head and neck

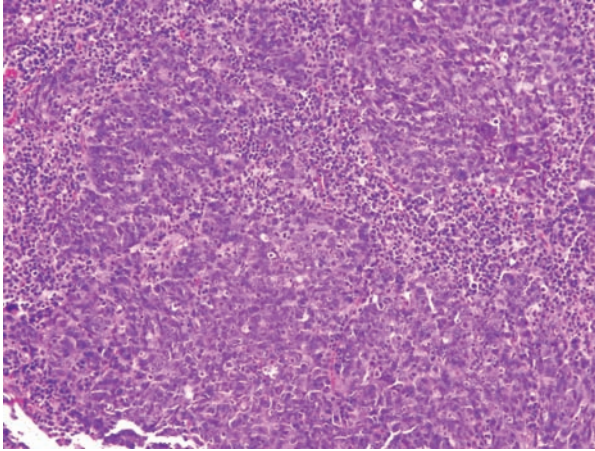
#### GROSS AND HISTOLOGIC FINDINGS:

- Gross: nonspecific firm, off-white tissue
- Architectural patterns include islands, solid syncytial sheets, and trabeculae of large epithelial cells with indistinct cell borders
- Epithelial cells have large smooth vesicular nuclei with nucleoli that are enlarged, distinct, single and eosinophilic, and modest amounts of eosinophilic cytoplasm; these cells are embedded in a rich lymphoplasmacytic stroma (**Figure 1-9**)
- Lymphocytes may surround islands of epithelial cells or infiltrate epithelial clusters fragmenting them into small groups
- Positive IHC: pan-cytokeratin, high-molecular-weight cytokeratin, Epstein–Barr virus; negative with cytokeratins 7 and 20.

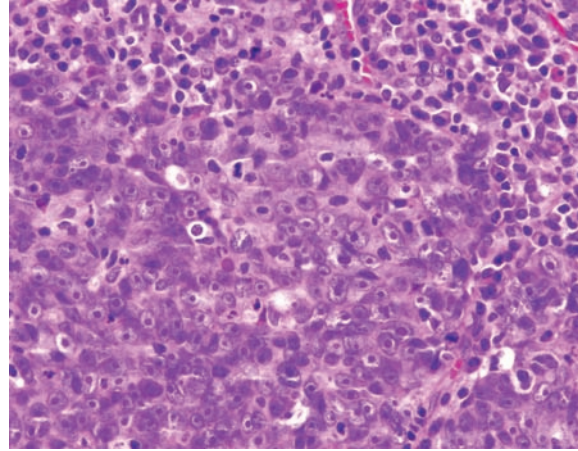
#### DIFFERENTIAL DIAGNOSIS:

- Large cell non-Hodgkin lymphoma
- Malignant melanoma

## Nasopharyngeal Carcinoma, Nonkeratinizing Undifferentiated Type



A



B

**FIGURE 1-9** *Nasopharyngeal Carcinoma, Nonkeratinizing Undifferentiated Type*

**A.** Lymphocytes and plasma cells surround and penetrate syncytial islands of malignant epithelial cells. **B.** Vesicular nuclei and large acidophilic nucleoli are typical of this undifferentiated carcinoma.

## Alveolar Soft Part Sarcoma

### DEFINITION:

Malignant mesenchymal neoplasm composed of very large, epithelioid cells arranged in solid nests or a loose pseudoalveolar pattern, and associated with a specific defect involving chromosome 17, der(17)t(X;17)(p11;q25).

### CLINICAL FEATURES:

- Rare; most common in 15- to 35-year-olds
- Head and neck region: orbit, oropharyngeal mucosa, and tongue are preferred sites
- Painless, slow-growing mass

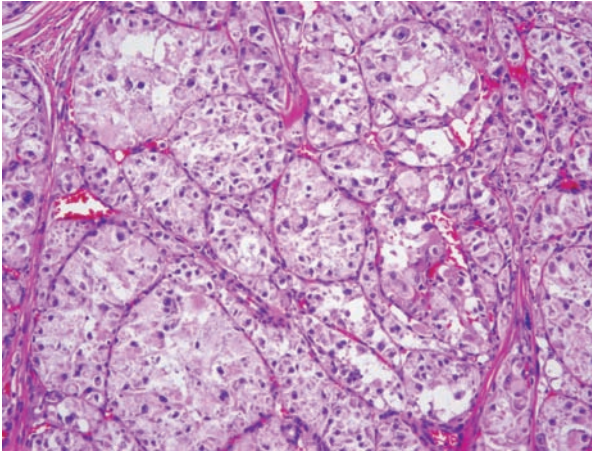
### GROSS AND HISTOLOGIC FINDINGS:

- Gross: soft, often friable mass
- Pseudoalveolar/nested pattern formed by sharply outlined cell nests relatively uniform in diameter and separated by thin fibrovascular septa; accompanied by a loss of cohesion among cells
- Rare solid pattern is more often seen in children
- Large, polygonal cells have abundant eosinophilic finely granular but occasionally clear cytoplasm, huge nuclei with single macronucleoli; occasional multiple nuclei per cell (**Figure 1-10**)
- PAS–diastase-resistant cytoplasmic crystalline structures vary in quantity, with some cases having numerous crystals while being rare or absent in others
- Mitoses and necrosis are infrequent, but vascular space invasion is common
- Positive IHC: TFE3 protein shows nuclear staining as a result of the x;17 unbalanced translocation. Variable staining occurs with vimentin, MyoD1, and actin; negative with epithelial and melanocytic markers.

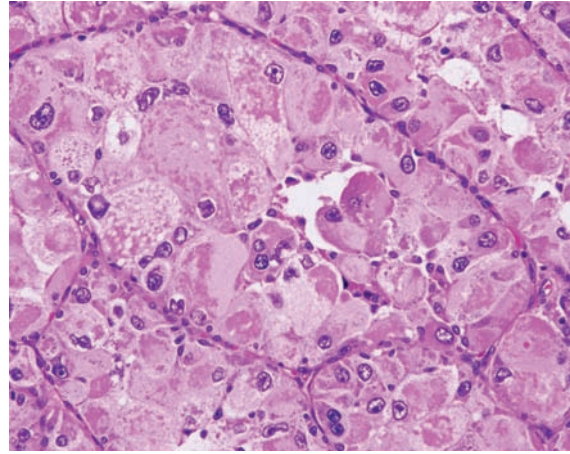
### DIFFERENTIAL DIAGNOSIS:

- Paraganglioma
- Granular cell tumor
- Adult rhabdomyoma
- Renal cell carcinoma

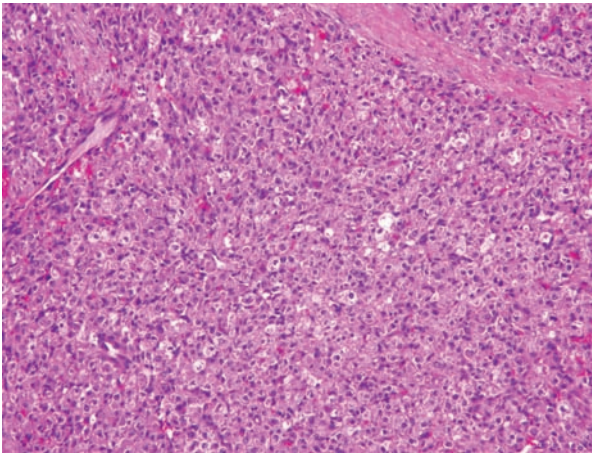
## Alveolar Soft Part Sarcoma



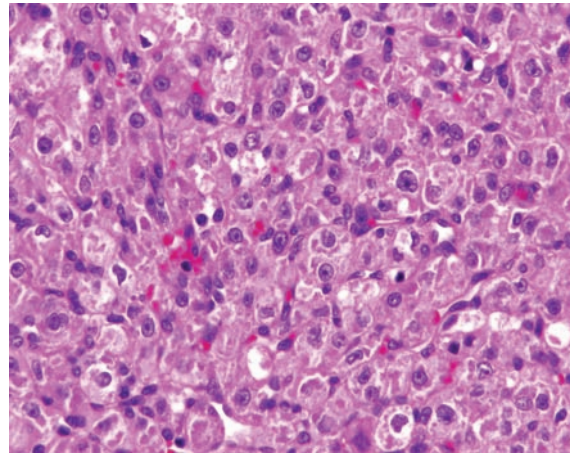
A



B



C



D

**FIGURE 1-10** *Alveolar Soft Part Sarcoma*

**A.** Thin capillaries interconnect with one another separating malignant cells into a nested/pseudoalveolar pattern. **B.** Malignant cells have voluminous oncocyte-like cytoplasm. **C.** This lingual example shows the nonalveolar or solid pattern seen in some pediatric examples. **D.** Eosinophilic clumps within cell cytoplasm represent crystalline material.



### Plasmablastic Lymphoma

#### DEFINITION:

Large cell lymphoma with morphologic features of immunoblasts, but with the immunophenotype of plasma cells.

#### CLINICAL FEATURES:

- Two to three percent of all HIV-related non-Hodgkin lymphomas; may occur in non-HIV-infected patients
- Forty to fifty years of age with an M:F ratio of 4–5:1
- Commonest sites include palate, gingival, and floor of mouth

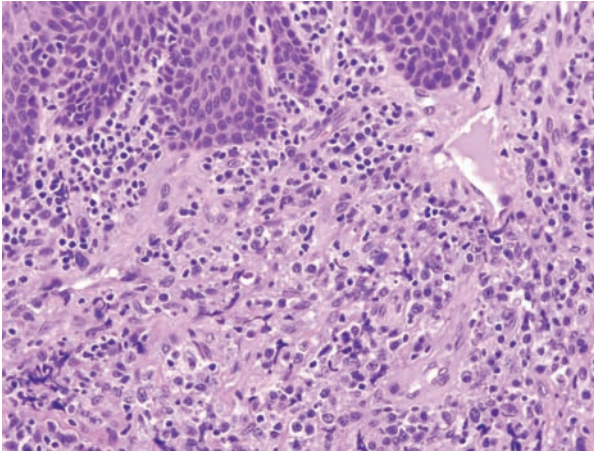
#### GROSS AND HISTOLOGIC FINDINGS:

- Gross: nonspecific firm, off-white tissue
- Solid pattern of growth with a variable “starry sky” pattern indicating a high mitotic index
- Immunoblast morphology shows coarse nuclear chromatin, a discrete enlarged nucleolus, and a modest amount of cytoplasm. Some cells show plasmacytic features with eccentric nuclear placement and perinuclear cytoplasmic clearing (**Figure 1-11**)
- Positive IHC: CD138, Vs38c, CD38, and EBER (by ISH); negative or weak with CD20, CD45, and PAX-5

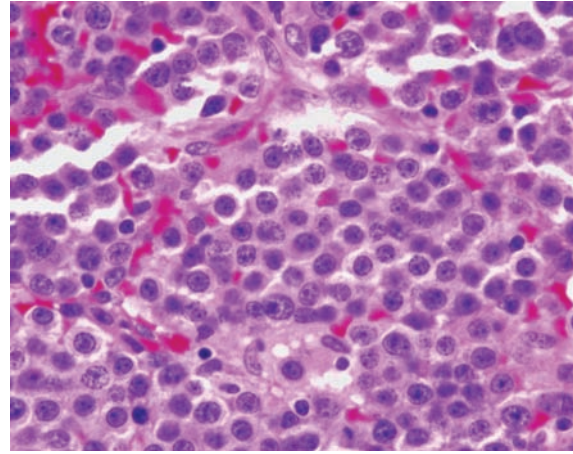
#### DIFFERENTIAL DIAGNOSIS:

- B-cell non-Hodgkin lymphomas
- Malignant melanoma

## Plasmablastic Lymphoma



A



B

**FIGURE 1-11** *Plasmablastic Lymphoma*

**A.** Malignant cells combine with small lymphocytes to focally hug the submucosa.

**B.** Cells with monotonously enlarged nuclei, visible nucleoli, and a modest amount of cytoplasm do not display overt plasmacytic features; note the binucleated cell at *top right*.

### Kaposi Sarcoma

#### DEFINITION:

Vascular tumor of intermediate malignancy universally associated with human herpes virus 8 (HHV-8) infection. The AIDS-related subtype is the most common encountered in the oral cavity.

#### CLINICAL FEATURES:

- Occurs in 15 to 20% of AIDS patients
- Peak incidence: 30 to 40 years of age
- Single or multiple raised, reddish-purple nodules on the mucosal surface with or without ulceration; nodules darken with age
- Common sites: palate, gingiva, dorsal surface of the tongue

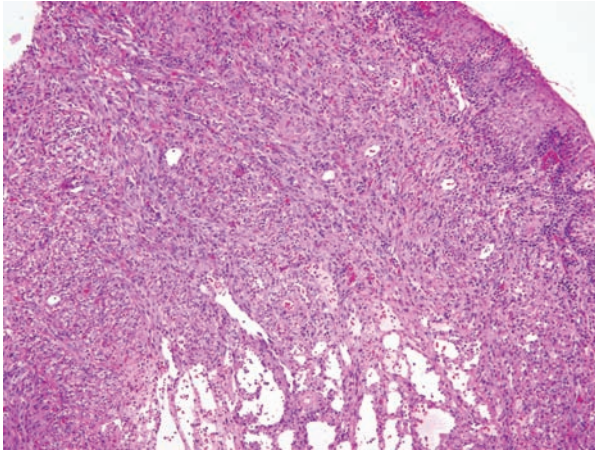
#### GROSS AND HISTOLOGIC FINDINGS:

- Early lesions show irregularly shaped, dilated blood vessels dissecting through stromal collagen without spindle cell population
- Mature lesions show a highly cellular proliferation of cytologically bland spindle cells accompanying blood vessels that have a slit-like configuration (**Figure 1-12**)
- Extravasated red cells, eosinophilic hyaline globules, and hemosiderin are common
- Necrosis and mitoses are infrequent
- Positive IHC: HHV-8, CD31, and CD34; negative with cytokeratin, melanoma markers

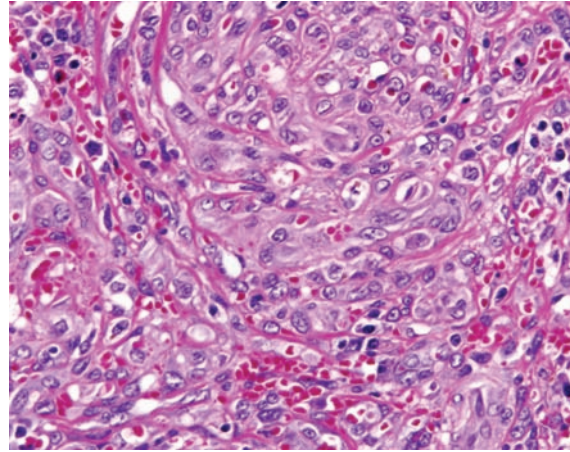
#### DIFFERENTIAL DIAGNOSIS:

- Hemangioma
- Other spindle cell sarcomas

## Kaposi Sarcoma



A



B

**FIGURE 1-12** *Kaposi Sarcoma*

**A.** Hypercellular spindle cell proliferation lies just below the mucosa; focal angiomatous change is present. **B.** Numerous extravasated red cells mix with malignant spindle and polygonal cells; a cluster of hyaline globules is in the center of the field.



## Nasal Cavity and Paranasal Sinuses

### NONNEOPLASTIC LESIONS

CHRONIC NONSPECIFIC SINUSITIS

SINONASAL POLYPS

ALLERGIC FUNGAL SINUSITIS (AFS)

FUNGAL SINUSITIS

### BENIGN NEOPLASMS

SCHNEIDERIAN PAPILLOMA

LOBULAR CAPILLARY HEMANGIOMA

[PYOGENIC GRANULOMA]

GLOMANGIOPERICYTOMA

SOLITARY FIBROUS TUMOR

### MALIGNANT NEOPLASMS

SINONASAL ADENOCARCINOMA (SNA), INTESTINAL TYPE

OLFACTORY NEUROBLASTOMA (ONB)

SINONASAL UNDIFFERENTIATED CARCINOMA [SNUC]

EXTRANODAL NK/T-CELL LYMPHOMA, NASAL TYPE

MUCOSAL MALIGNANT MELANOMA

RHABDOMYOSARCOMA (RMS)



### Chronic Nonspecific Sinusitis

#### DEFINITION:

Chronic rhinosinusitis (vasomotor rhinosinusitis) is a reaction to a multitude of insults including allergy, various medications, environmental exposure, and idiopathic.

#### CLINICAL FEATURES:

- Nonspecific symptoms include nasal discharge, headache, nasal congestion, and sneezing
- No age predilection
- Radiologic features include mucosal thickening and, if severe, sinus opacification

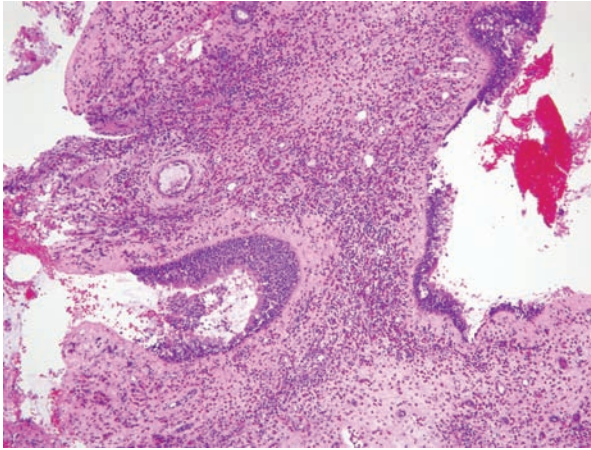
#### GROSS AND HISTOLOGIC FINDINGS:

- Tissue fragments often admixed with blood; no helpful gross features
- Sinonasal mucosa is normal or may undergo squamous metaplasia. An edematous stroma contains a mixed inflammatory infiltrate typically dominated by lymphocytes and plasma cells with a variable number of eosinophils and neutrophils (**Figure 2-1**)
- Minimal stromal fibrosis and no necrosis
- If necessary, flow cytometry shows polyclonality and IHC shows both B- and T-cell markers

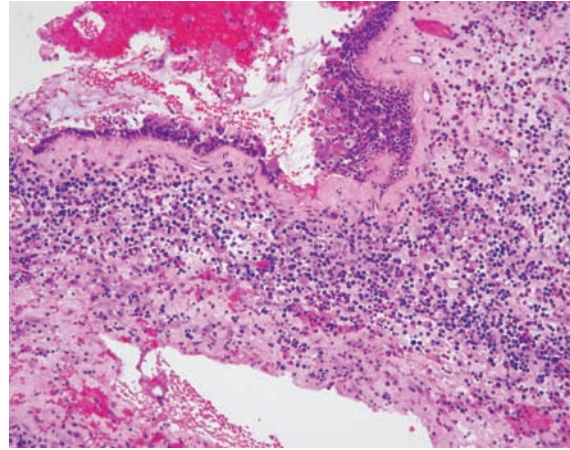
#### DIFFERENTIAL DIAGNOSIS:

- Small cell non-Hodgkin lymphoma
- Inflammatory polyp

## Chronic Nonspecific Sinusitis



A



B

**FIGURE 2-1** *Chronic Nonspecific Sinusitis*

**A.** Slightly edematous sinonasal stroma is filled with an intense mixed inflammatory infiltrate. The mucosa is unremarkable. **B.** Note basement membrane thickening and focal denudation of ciliated mucosa.

### Sinonasal Polyps

#### DEFINITION:

Polypoid masses that develop in the nasal cavity or paranasal sinuses as a consequence of various etiologies including allergic rhinitis, cystic fibrosis, and aspirin sensitivity/intolerance. Polyps that expand through the maxillary antrum into the nasopharynx or nasal cavity are termed antrochoanal polyps.

#### CLINICAL FEATURES:

- Similar to those of vasomotor rhinosinusitis
- No specific laboratory tests; however, children with this entity should be tested to exclude cystic fibrosis

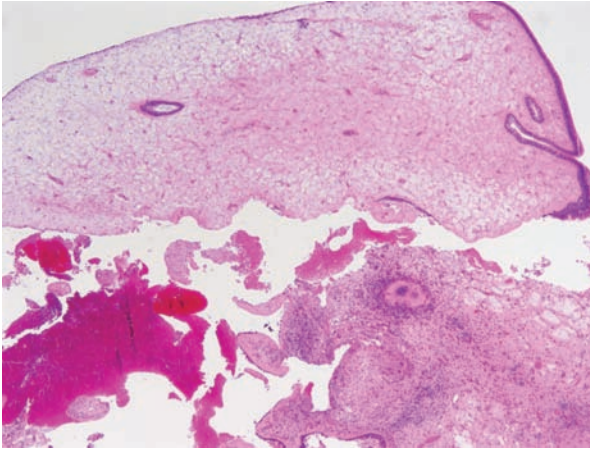
#### GROSS AND HISTOLOGIC FINDINGS:

- Gross: smooth almost translucent polypoid mass; cut surface is flat, glistening, and homogeneously gelatinous
- Ciliated surface epithelium with or without squamous metaplasia and thickened basement membrane
- Edematous stroma with lymphoplasmacytic infiltrate, and variable eosinophils and neutrophils (**Figure 2-2**)
- Reactive stromal atypia and fibrosis more common with antrochoanal polyp
- Infarction, surface ulcer with granulation tissue all possible

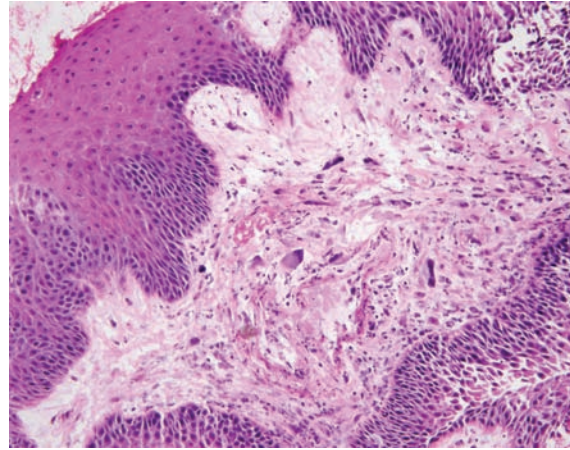
#### DIFFERENTIAL DIAGNOSIS:

- Mucus retention cyst
- Angiofibroma
- Nasopharyngeal angiofibroma
- Embryonal rhabdomyosarcoma, botryoid type

## Sinonasal Polyps



A



B

**FIGURE 2-2** *Sinonasal Polyps*

**A.** A markedly edematous polyp with minimal inflammation and small branching capillaries. **B.** Stromal atypia highlighted by nuclear enlargement and hyperchromasia is present. The mucosal surface has undergone squamous metaplasia.

### Allergic Fungal Sinusitis (AFS)

#### DEFINITION:

An allergic reaction secondary to fungi that leads to the formation of so-called allergic mucin. This reaction is thought to be perpetuated by the intense eosinophilic infiltrate that accompanies this condition.

#### CLINICAL FEATURES:

- Nonspecific symptoms of vasomotor rhinosinusitis
- Additionally will have peripheral eosinophilia and an elevated IgE to fungal antigens

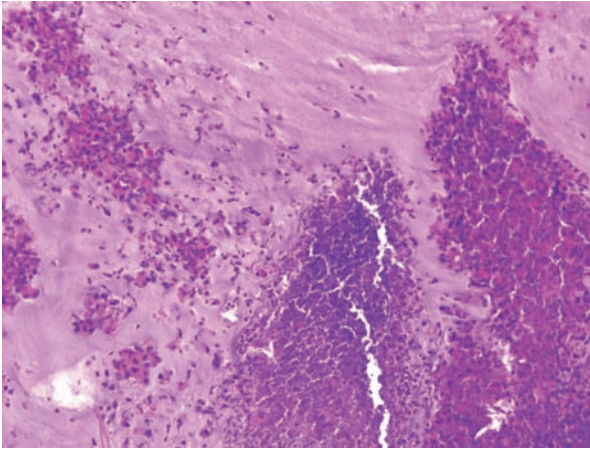
#### GROSS AND HISTOLOGIC FINDINGS:

- Gross: soft, often malodorous brown or greenish-brown and putty-like, sometimes thick, tenacious with clay-like consistency
- Combination of laminated mucin layers with large numbers of eosinophils with or without Charcot-Leyden crystals and cytoplasmic debris comprise “allergic mucin” (Figure 2-3)
- Histochemical stain often necessary to identify fungal organisms comprised primarily of dermatiaceous fungi and *Aspergillus* sp.
- Absence of necrosis

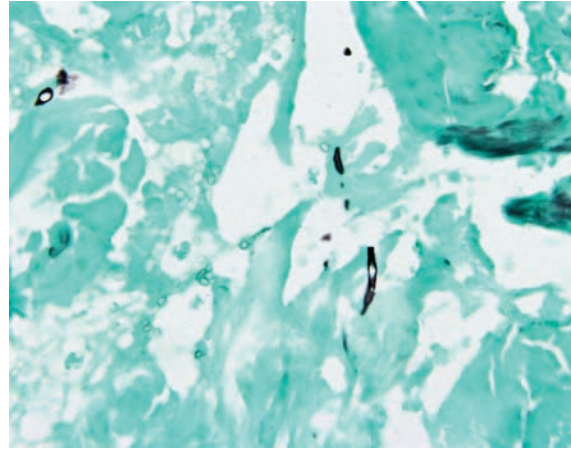
#### DIFFERENTIAL DIAGNOSIS:

- Invasive fungal sinusitis
- Chronic rhinosinusitis
- Mucocoele

## Allergic Fungal Sinusitis (AFS)



A



B

**FIGURE 2-3** *Allergic Fungal Sinusitis*

**A.** Inspissated clusters of degenerating inflammatory cells (principally eosinophils) are surrounded by thick mucin. **B.** Fragments segments of fungal hyphae are emphasized in this GMS stain.



### Fungal Sinusitis

#### DEFINITION:

Two major forms of nonallergic fungal sinusitis exist: (1) mycetoma (fungus ball), a noninvasive aggregate of fungal forms with a minimal inflammatory response, absent necrosis, and absent allergic mucin, and (2) acute invasive fungal sinusitis (IFS), which constitutes a medical emergency and is characterized by a destructive, potentially lethal invasion of tissue by fungi in the *Aspergillus* spp. and Mucorales order (*Mucor*, *Absidia*, and *Rhizopus* spp.).

#### CLINICAL FEATURES:

- Headache, pain, nasal discharge, facial swelling, proptosis, foul smelling
- Immunocompromised host (diabetes, AIDS) typical for IFS

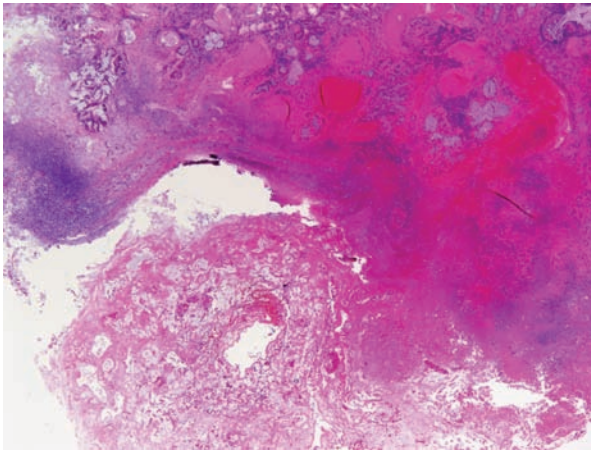
#### GROSS AND HISTOLOGIC FINDINGS:

- Gross: IFS consists of soft hemorrhagic gangrenous tissue fragments
- IFS shows extensive necrosis, thrombosis, hemorrhage, acute inflammation, and fungal hyphae with angioinvasion (**Figure 2-4, A–C**)
- Mycetoma consists of a mass of interconnecting hyphae lacking the inflammation and destructive tissue response of IFS. Calcium oxalate crystals sometimes present (**Figure 2-4D**)
- Fungi are usually visible with H&E stain, but silver stain such as GMS (Gomori methenamine silver stain) is very useful in organism identification
- *Aspergillus* (branching at 45° angles, septated hyphae) seen in both forms; Mucorales (broad nonseptated, twisted, branching at random angles) more often associated with IFS

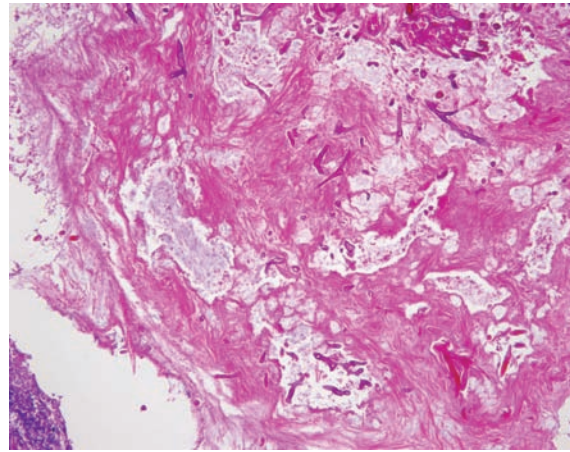
#### DIFFERENTIAL DIAGNOSIS:

- Allergic fungal sinusitis
- Wegener granulomatosis

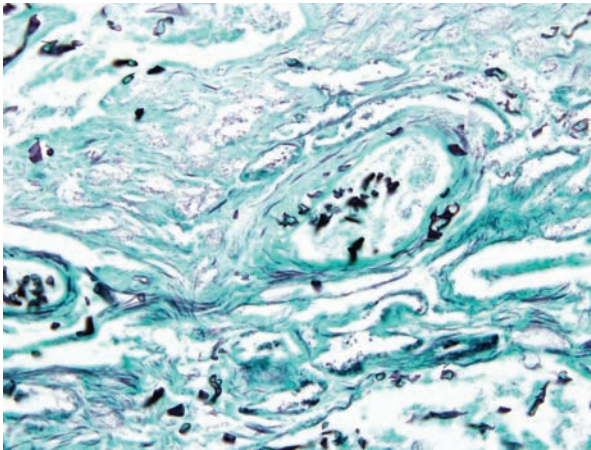
## Fungal Sinusitis



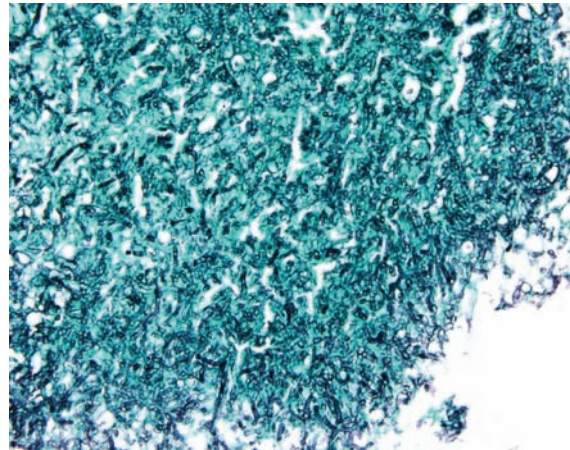
A



B



C



D

**FIGURE 2-4** *Fungal Sinusitis*

**A.** Invasive fungal sinusitis shows extensive tissue necrosis, hemorrhage, and acute inflammation. **B.** IFS: Randomly branching nonseptated fungal hyphae are seen in this necrotic tissue. **C.** Angioinvasion by fungi is appreciated in this GMS stain.

**D.** Mycetoma: a thick mat of septated *Aspergillus* hyphae elicits no inflammatory response (GMS stain).

### Schneiderian Papilloma

#### DEFINITION:

Benign papillomatous neoplasm that arises from specialized Schneiderian mucosa that lines much of the nasal cavity except for the vestibule and superior wall in middle-aged adults.

#### CLINICAL FEATURES:

- Headache, rhinorrhea, epistaxis, and nasal obstruction
- Polypoid mass with sinus opacification and sometimes bony erosion

#### GROSS AND HISTOLOGIC FINDINGS:

- Three histopathologic types: exophytic (fungiform), endophytic (inverted), and oncocytic (cylindrical cell).

##### Exophytic [Fungiform] Papilloma

- Males are more commonly afflicted
- Arises primarily from the nasal septum
- Gross: broad cauliflower-like projections, up to 2 cm
- Wide papillary projections with an inner fibrovascular core (**Figure 2-5A**)
- Lined by well-differentiated squamous epithelium up to 20 cells thick; may be minimally keratinized and contain goblet cells
- Rare mitoses

##### Endophytic [Inverted] Papilloma

- Males more commonly affected
- Arises from lateral nasal wall (not septum), and occasionally paranasal sinuses
- Gross: firm, polypoid with a clefted outer surface
- Inverted pattern of benign squamous and transitional-type nonkeratinizing mucosa with well-demarcated rounded epithelial islands within stroma (**Figure 2-5B,C**)
- Loose, myxoid stroma with variable inflammatory infiltrate
- Transformation to squamous carcinoma in up to 11% of cases; rare in other types
- Lacks stromal seromucinous glands

##### Oncocytic Schneiderian [Cylindrical Cell] Papilloma

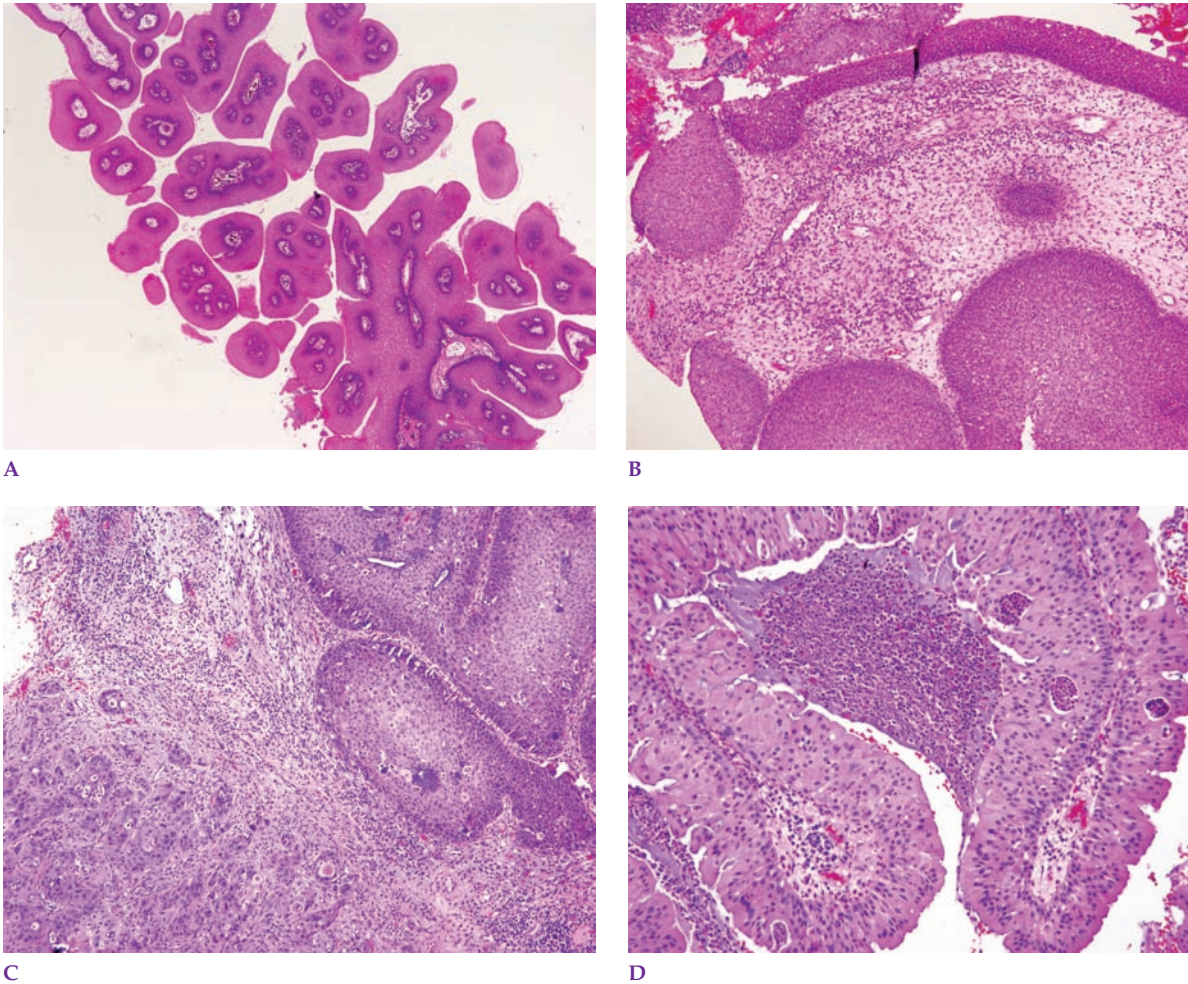
- No gender preference; rarest form of Schneiderian papilloma
- Arises exclusively on lateral nasal wall or sinuses
- Gross: polypoid, tan, red-brown, often received fragmented
- Exophytic and endophytic ribbons of oncocytic columnar cells with intraepithelial microabscesses (**Figure 2-5D**)

#### DIFFERENTIAL DIAGNOSIS:

- Well-differentiated squamous carcinoma arising in papilloma papillary squamous carcinoma
- Sinonasal polyp with squamous metaplasia
- For oncocytic Schneiderian papilloma: rhinosporidiosis



## Schneiderian Papilloma



**FIGURE 2-5** *Schneiderian Papilloma*

**A.** Exophytic papilloma shows an en face section with multiple branching papillae lined by multiple layers of bland squamous mucosa. **B.** Inverted papilloma: bulbous squamous epithelium projects downward into inflamed edematous stroma. **C.** An invasive squamous carcinoma (*lower left*) arises in association with this inverted papilloma (*upper right*). **D.** Oncocytic Schneiderian papilloma: Papillary epithelium containing neutrophilic microabscesses is lined by several layers of oncocytic cells.

### Lobular Capillary Hemangioma [Pyogenic Granuloma]

#### DEFINITION:

Benign polypoid proliferation of capillaries with limited growth potential and accompanied by inflammation and ulceration of the mucosal surface.

#### CLINICAL FEATURES:

- Broad age range
- Can occur in a variety of sites including lips, gingival, tongue, and palate
- Symptoms including bleeding due to friability of the lesion

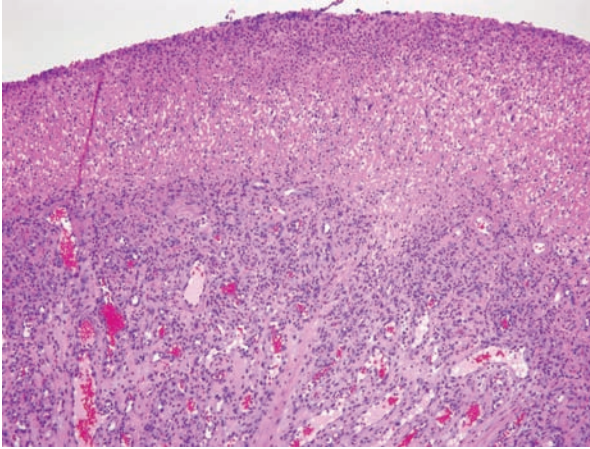
#### GROSS AND HISTOLOGIC FINDINGS (Figure 2-6A):

- Gross: exophytic erythematous lobulated, sessile, or pedunculated polyp
- Closely clustered capillaries are in a lobular arrangement with flat or cuboidal endothelial cells that lack cytologic atypia (**Figure 2-6B**)
- Mucosa partially envelops the polyp and is commonly superficially ulcerated
- Variable number of acute and chronic inflammatory cells
- Positive IHC: CD31, CD34 in endothelial cell cytoplasm

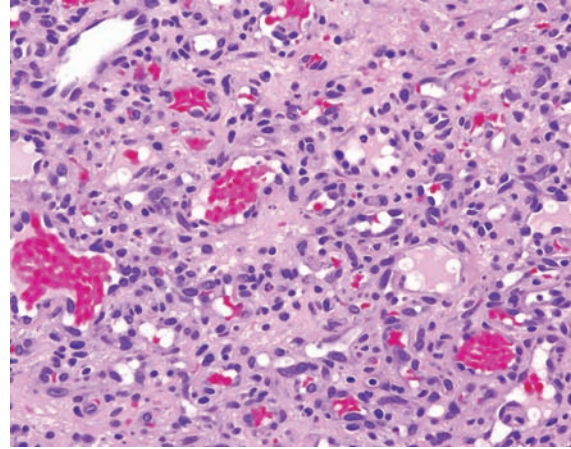
#### DIFFERENTIAL DIAGNOSIS:

- Granulation tissue
- Glomangiopericytoma

## Lobular Capillary Hemangioma [Pyogenic Granuloma]



A



B

**FIGURE 2-6** *Lobular Capillary Hemangioma [Pyogenic Granuloma]*

**A.** Typical for this lesion is an ulcerated surface consisting of a layer of fibrin and degenerating inflammatory cells. **B.** Blood and serum-filled capillaries are lined by flattened and cuboidal endothelial cells.



### Glomangiopericytoma

#### DEFINITION:

Benign mesenchymal neoplasm of the nasal cavity and paranasal sinuses that demonstrates perivascular myoid differentiation.

#### CLINICAL FEATURES:

- Rare, <1% of all sinonasal tumors; broad age range from infants to elderly with most patients in decades 6 and 7
- Nonspecific symptoms include nasal obstruction, headache, nasal discharge, epistaxis
- Site: lateral wall of the nasal cavity

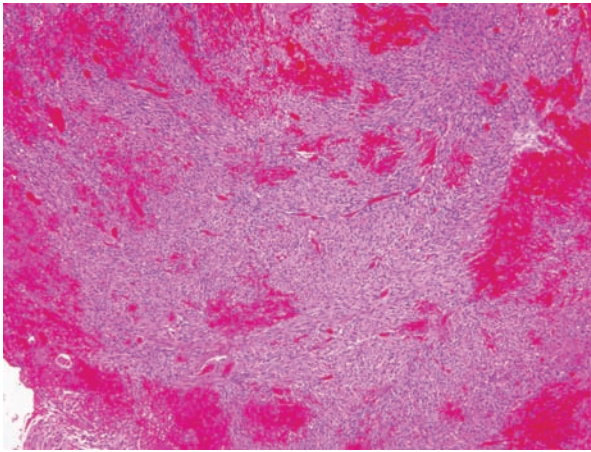
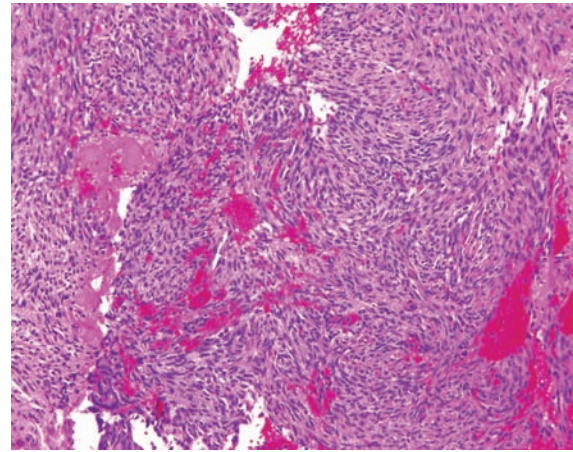
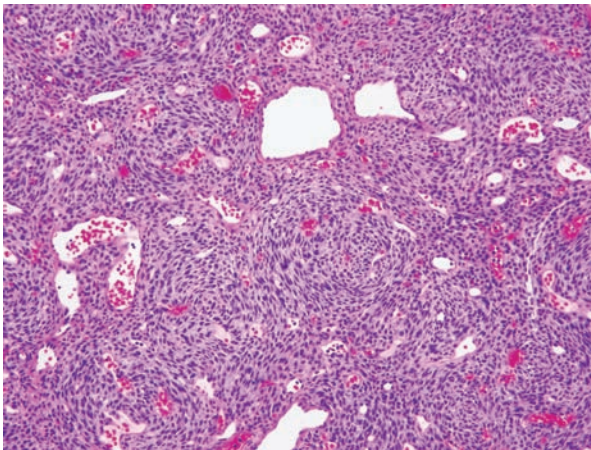
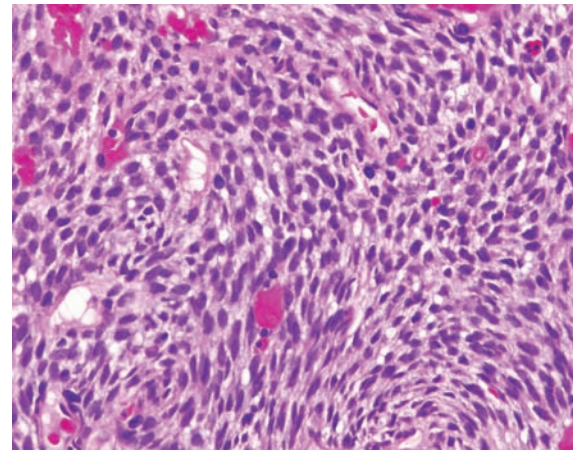
#### GROSS AND HISTOLOGIC FINDINGS:

- Well-circumscribed proliferation of oval and spindle cells containing numerous vascular channels, but lacking a fibrous capsule
- Cells arranged in syncytial fascicles with short storiform, whorled, or palisaded patterns (**Figure 2-7**)
- Monomorphic cell nuclei have smooth contours, evenly dispersed chromatin, and lack nucleoli
- Small to intermediate-sized vessels often show “hemangiopericytomatous”-type branching, perivascular hyalinization
- Necrosis is absent and mitotic activity is minimal
- Positive IHC: smooth muscle actin, muscle specific actin, factor XIIIa; negative staining with bcl-2 and CD34.

#### DIFFERENTIAL DIAGNOSIS:

- Solitary fibrous tumor
- Lobular capillary hemangioma
- Monophasic synovial sarcoma

## Glomangiopericytoma

**A****B****C****D**

**FIGURE 2-7** *Glomangiopericytoma*

**A.** A hemorrhagic fragment consists of a solid sheet of swirling spindle cells. **B.** A vague whorled pattern is present without necrosis or inflammation. **C.** Vessels with minimal branching are more conspicuous in this case. **D.** Monotonous rounded, oval nuclei lack discernible nucleoli. Note the whorled pattern at *lower right*.

### Solitary Fibrous Tumor

#### DEFINITION:

Ubiquitous benign mesenchymal neoplasm characterized by a nonspecific branching vascular pattern and universal staining with CD34.

#### CLINICAL FEATURES:

- Rare in the head and neck; sites other than the sinonasal cavity include salivary glands, meninges, nasopharynx, and periorbital soft tissue
- Broad age range with median age 50 to 60 years; males and females equally affected
- Nonspecific symptoms include epistaxis and nonspecific complaints of nasal obstruction

#### GROSS AND HISTOLOGIC FINDINGS:

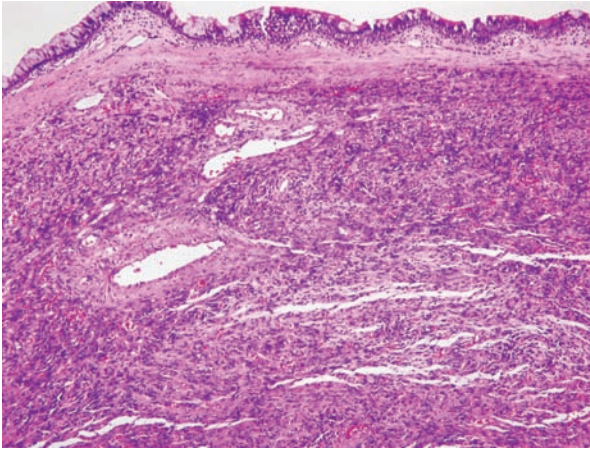
- Usually circumscribed but not encapsulated
- Proliferation of rounded and spindle cells arranged in alternating hypercellular and hypocellular zones without demonstrating a specific pattern
- Variable amount of collagen, often thick and “rope-like,” and myxoid change (**Figure 2-8**)
- Vessels have a staghorn, “hemangiopericytomatous”-type branching pattern
- Cells have bland, smoothly contoured elongated or rounded nuclei and a small amount of cytoplasm with indistinct borders
- Mitoses are usually <2 mf per 10 hpf
- Positive IHC: CD34, bcl-2, and CD99; negative for pan-cytokeratin, S-100, smooth muscle actin, muscle specific actin, and desmin

#### DIFFERENTIAL DIAGNOSIS:

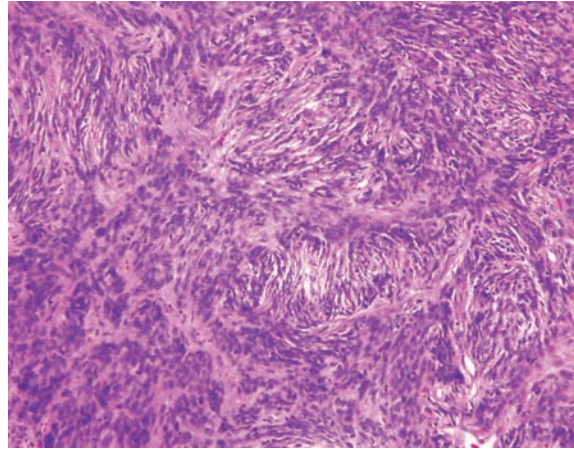
- Glomangiopericytoma
- Schwannoma
- Leiomyoma



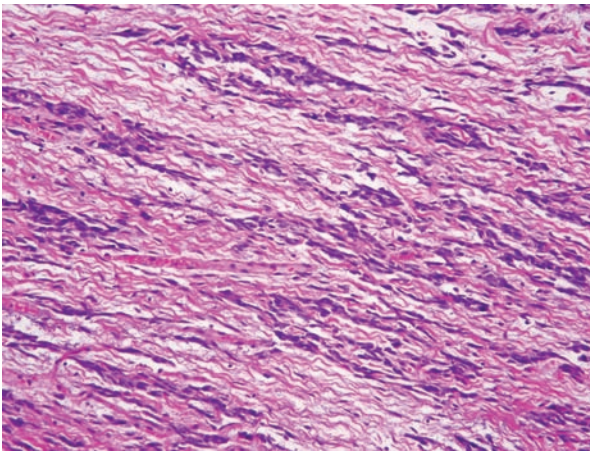
## Solitary Fibrous Tumor



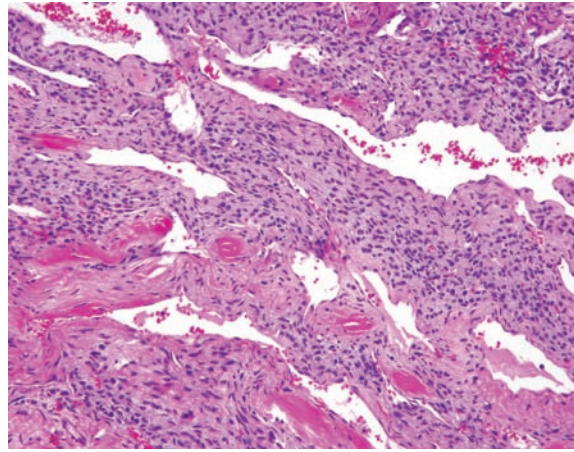
A



B



C



D

**FIGURE 2-8** *Solitary Fibrous Tumor*

**A.** A nonencapsulated proliferation of spindle cells is narrowly separated from overlying sinonasal mucosa. **B.** A highly cellular focus shows a short storiform pattern. **C.** This less cellular, more collagenized focus contains cords of spindle cells. **D.** Widely patent anastomosing vessels create a “hemangiopericytomatous” vascular pattern.

### Sinonasal Adenocarcinoma (SNA), Intestinal Type

#### DEFINITION:

Malignant glandular tumor primary to the nasal cavity and paranasal sinuses.

#### CLINICAL FEATURES:

- Sporadic and occupational (woodworking, leather dust) forms
- Arises in nasal cavity and paranasal sinuses
- Unilateral nasal obstruction, epistaxis

#### GROSS AND HISTOLOGIC FINDINGS:

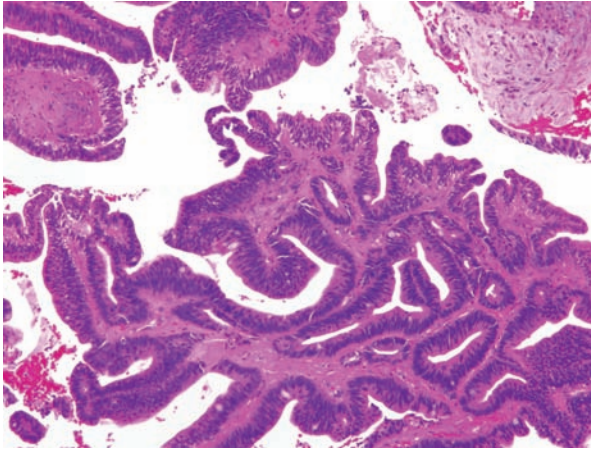
- Gross: papillary, polypoid friable tissue fragments
- Histologic variants: papillary, colonic, solid, mucinous, mixed
- Papillary type: papillae lined by nonciliated columnar cells with admixed goblet cells resembling intestinal mucosa; colonic type: tubuloglandular pattern without papillae; solid type: solid, trabecular cords with little gland formation; mucinous type: glands distended with mucus and/or strips of epithelial cells or signet ring cells embedded in large pools of mucin (**Figure 2-9**)
- Positive IHC: pan-keratin, CK7, CK20, CDX2, villin

#### DIFFERENTIAL DIAGNOSIS:

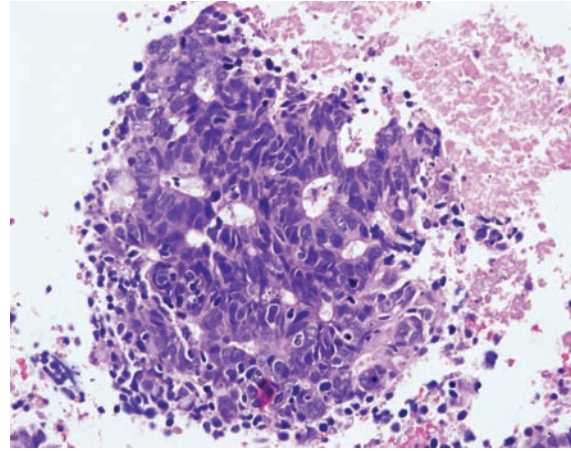
- Colorectal carcinoma metastasis



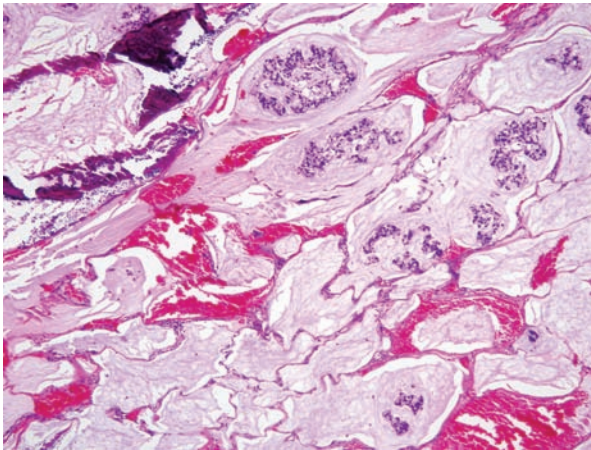
## Sinonasal Adenocarcinoma (SNA), Intestinal Type



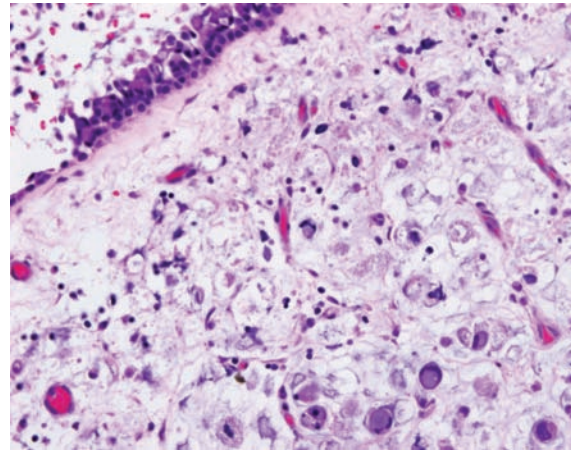
A



B



C



D

**FIGURE 2-9** *Sinonasal Adenocarcinoma (SNA), Intestinal Type*

**A. Papillary Variant.** Malignant glands lined by hyperstratified cells with a papillary pattern imitate a colonic villous adenoma. **B. Colonic Variant.** Malignant glands in a back-to-back arrangement show cell necrosis and surrounding debris. **C. Mucinous Goblet Cell Variant.** Bland cell clusters are set in large mucin pools. **D. Mucinous Signet Ring Cell Variant.** Mucinous stroma harbors malignant single cells with amphiphilic mucin-filled cytoplasm and an eccentrically positioned nucleus.



### Olfactory Neuroblastoma (ONB)

#### DEFINITION:

Malignant neuroectodermal neoplasm associated with and believed to arise from specialized olfactory mucosa/membrane in the superior nasal septum, superior turbinate, and cribriform plate.

#### CLINICAL FEATURES:

- Occurs in young to middle-aged adults, but a broad age range exists
- Symptoms include unilateral nasal obstruction, epistaxis, visual symptoms, and headache

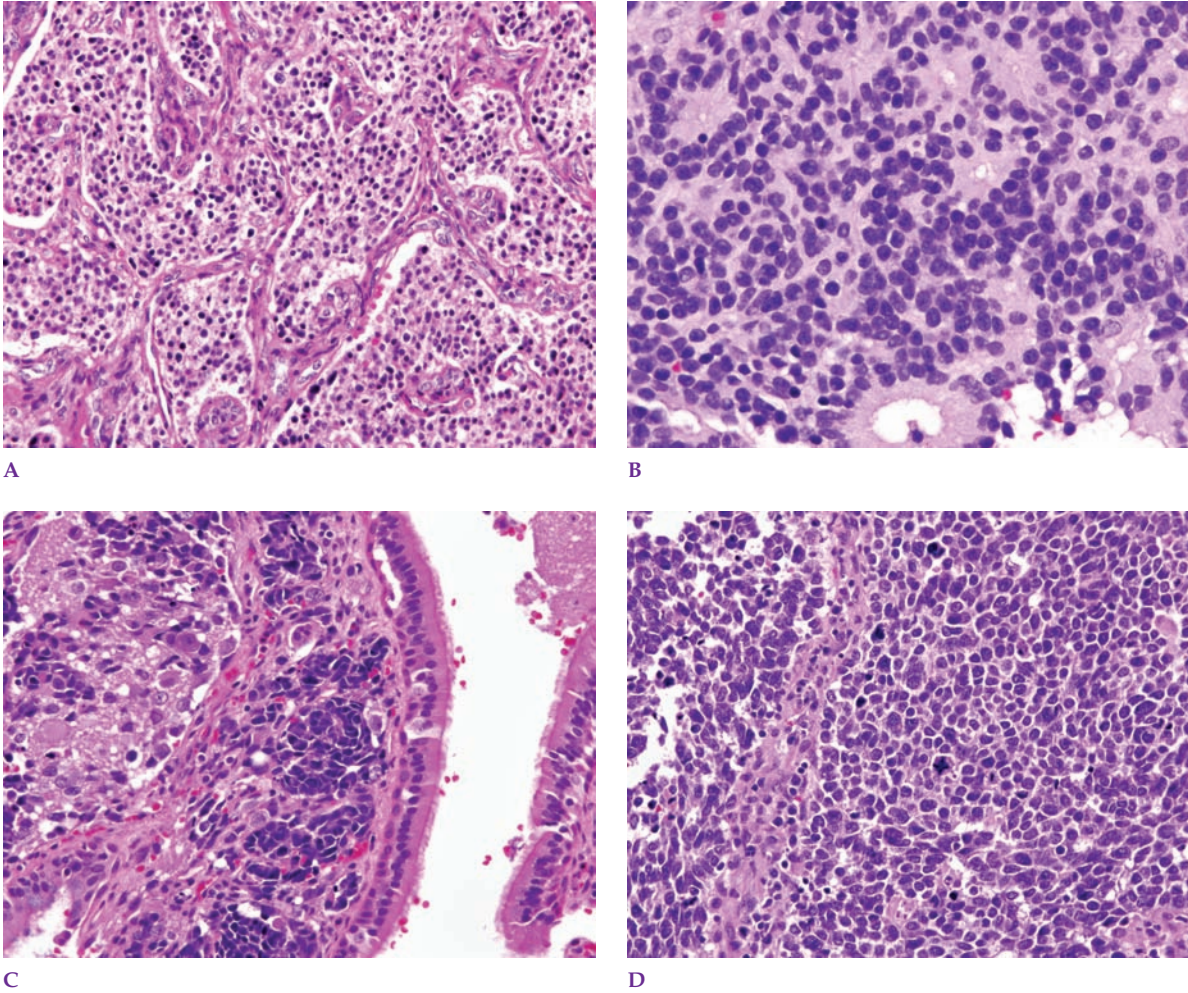
#### GROSS AND HISTOLOGIC FINDINGS:

- Small to intermediate-sized cells are in nests, sheets with coarse nuclear chromatin, and minimal cytoplasm
- Low-grade ONB (grades 1 and 2): lobular pattern, rare mitosis, neurofibrillary matrix, and Homer-Wright type rosettes (**Figure 2-10 A-C**)
- High-grade ONB (grades 3 and 4): more solid pattern, larger nuclei, increased pleomorphism, necrosis, mitoses, and lacks neurofibrillary matrix (**Figure 2-10 D.**)
- Ganglionic, glandular, melanocytic, and myogenic differentiation are possible (**Figure 2-10 C.**)
- Positive IHC: NSE, CD56, synaptophysin, chromogranin (focal, weak). S-100 staining seen in sustentacular cells in low-grade ONB. Negative staining with EMA, CEA, and CD99. Pan-cytokeratin may show focal staining

#### DIFFERENTIAL DIAGNOSIS:

- Non-Hodgkin lymphoma
- Basaloid squamous cell carcinoma
- Sinonasal undifferentiated carcinoma
- Small cell neuroendocrine carcinoma
- Ewing sarcoma and other malignant small round cell tumors

## Olfactory Neuroblastoma (ONB)



**FIGURE 2-10** *Olfactory Neuroblastoma*

**A.** Small cells in a pseudo-alveolar/nested pattern are separated by a delicate fibrillar matrix. **B.** Homer-Wright rosettes surround neuropil while Flexner-Wintersteiner type rosettes contain a central lumen. Note the lack of distinct nucleoli. **C.** Ganglion cell differentiation (*upper left*) is mixed with primitive neuroblasts sitting below the mucosa. **D.** High-grade ONB shows a solid sheet of cells with many mitoses including atypical mitotic figures.

### Sinonasal Undifferentiated Carcinoma [SNUC]

#### DEFINITION:

High-grade carcinoma (survival <5 years) involving the nasal cavity and paranasal sinuses and showing no evidence of squamous or glandular differentiation.

#### CLINICAL FEATURES:

- Young adults to elderly; median age 50 years; M/F ratio = 2–3:1
- Nonspecific symptoms include unilateral nasal obstruction, epistaxis, visual symptoms, and headache

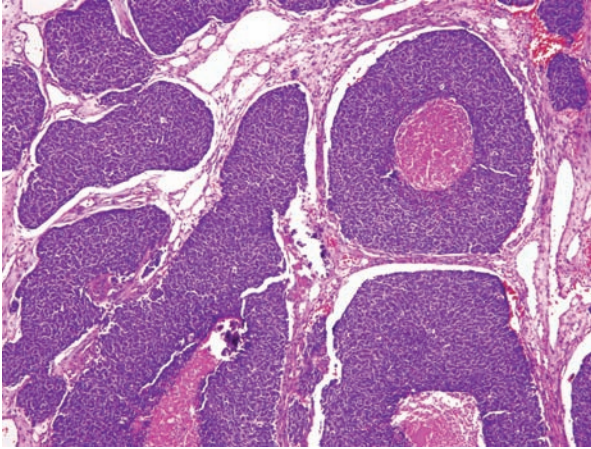
#### GROSS AND HISTOLOGIC FINDINGS:

- Solid sheets, broad trabeculae, and large nests of medium-size to large cells; comedo-like central necrosis occurs within nests and growth along the mucosa and in vessels (**Figure 2-11**)
- Large oval nuclei, ± enlarged nucleoli, minimal cytoplasm, and frequent mitoses including atypical mitotic figures
- Positive IHC: pan-cytokeratin, EMA (50%); CEA, EBV negative. Rare synaptophysin positive

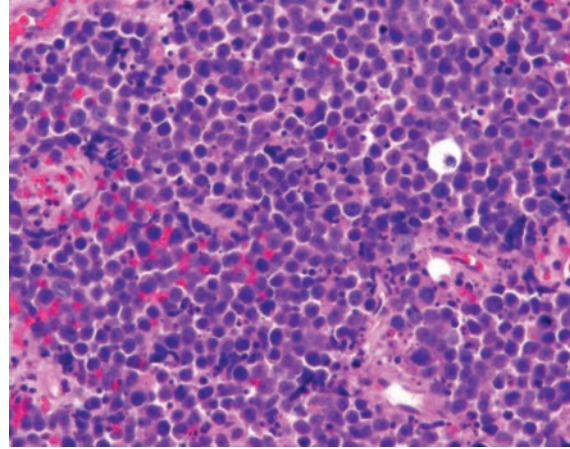
#### DIFFERENTIAL DIAGNOSIS:

- Non-Hodgkin lymphoma, large cell
- Adenoid cystic carcinoma, solid variant
- Basaloid squamous cell carcinoma
- Olfactory neuroblastoma, high grade

## Sinonasal Undifferentiated Carcinoma [SNUC]



A



B

**FIGURE 2-11** *Sinonasal Undifferentiated Carcinoma*

**A.** Lobular nests of carcinoma contain central comedo-type necrosis. **B.** Large cells contain discrete nucleoli and minimal cytoplasm. Individually necrotic cells are sprinkled throughout.



### Extranodal NK/T-cell Lymphoma, Nasal Type

#### DEFINITION:

High-grade extranodal non-Hodgkin lymphoma expressing NK-cell and cytotoxic T-cell phenotype involving multiple sites in the upper aerodigestive tract including nasal cavity, nasopharynx, and paranasal sinuses.

#### CLINICAL FEATURES:

- Primarily affects Asians and Hispanic populations of Central and South America
- Strongly associated with EBV
- Nonspecific symptoms include nasal obstruction, epistaxis, nasal and orbital swelling, and palatal destruction

#### GROSS AND HISTOLOGIC FINDINGS:

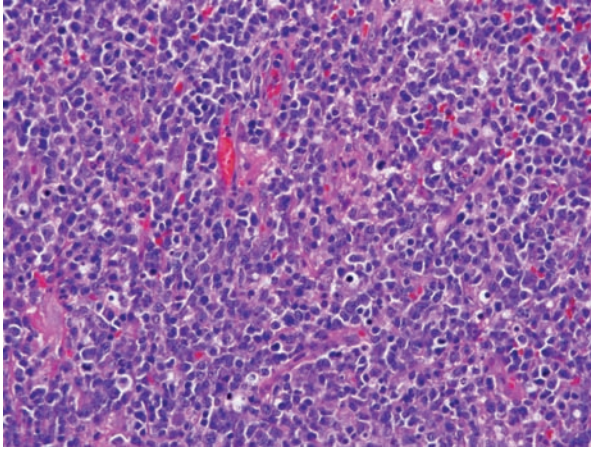
- Mucosal ulcers with solid sheets of lymphocytes having a wide spectrum of cell size; large cells may predominate
- Necrosis and vascular involvement showing an angiocentric and angiodestructive pattern and fibrinoid necrosis of vessel walls common (**Figure 2-12**)
- Foci of pseudoepitheliomatous squamous hyperplasia
- Positive IHC: CD56, CD2, cytoplasmic CD3ε, granzyme B, TIA, EBER diffusely; other T-cell antigens typically negative

#### DIFFERENTIAL DIAGNOSIS:

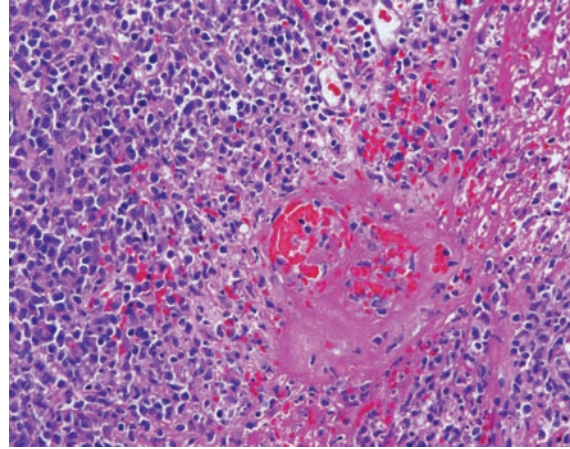
- Other forms of non-Hodgkin lymphoma particularly diffuse large B-cell, Burkitt, and plasmablastic lymphoma
- Adenoid cystic carcinoma, solid variant
- Sinonasal undifferentiated carcinoma
- Olfactory neuroblastoma, high grade



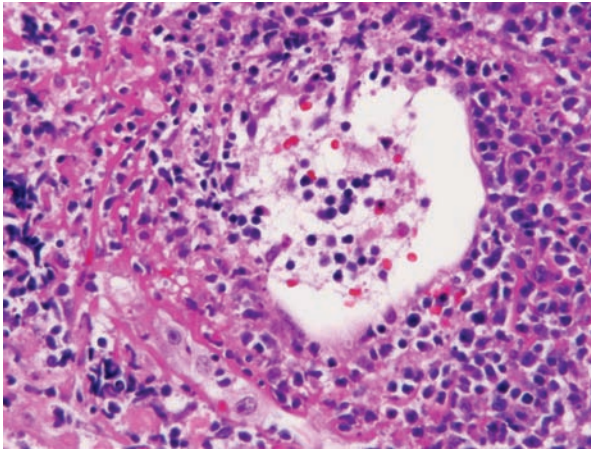
## Extranodal NK/T-cell Lymphoma, Nasal Type



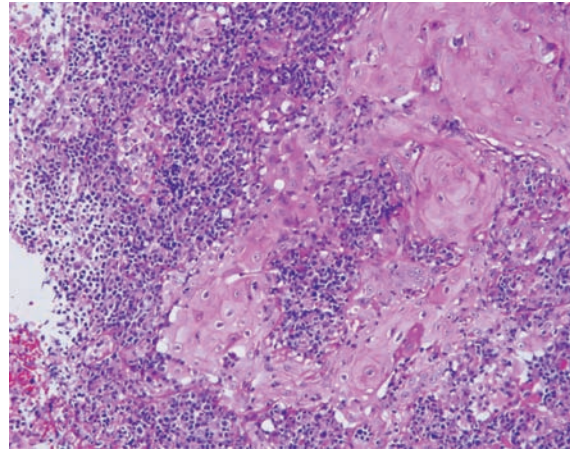
A



B



C



D

**FIGURE 2-12** *Extranodal NK/T-Cell Lymphoma, Nasal Type*

**A.** A mixture of small, intermediate and large lymphocytes are present.

**B.** Fibrinoid necrosis surrounds this partially thrombosed necrotic vessel. **C.** The angioinvasive quality of this lymphoma is seen along with fibrinoid necrosis.

**D.** Pseudoepitheliomatous squamous hyperplasia may be confused for squamous carcinoma.

### Mucosal Malignant Melanoma

#### DEFINITION:

Malignant neoplasm of melanocytes or melanocytic precursors arising at the mucosal–stromal interface. Sinonasal melanoma is rare.

#### CLINICAL FEATURES:

- Typically elderly patients with a broad age range and no gender preference
- Arises in nasal cavity and paranasal sinuses, but may occur in other extracutaneous head and neck sites
- Nonspecific symptoms include nasal obstruction, facial pain, and epistaxis

#### GROSS AND HISTOLOGIC FINDINGS:

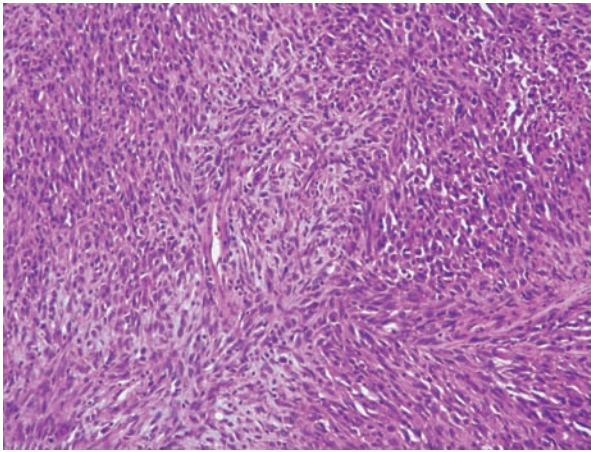
- Gross: often grossly polypoid, ulcerated, and pigmented on cut surface
- Melanoma is deservedly quoted as the “great imitator” due a range of cell shapes, most often epithelioid but also spindle, rhabdoid, small cell, and anaplastic histology (**Figure 2-13**)
- Melanin pigment varies from finely granular to large chunk-like fragments and is scattered in malignant cells and melanophages
- Positive IHC: S-100, HMB45 (gp100), Melan-A, tyrosinase; negative for epithelial, lymphoid, and myogenic markers

#### DIFFERENTIAL DIAGNOSIS:

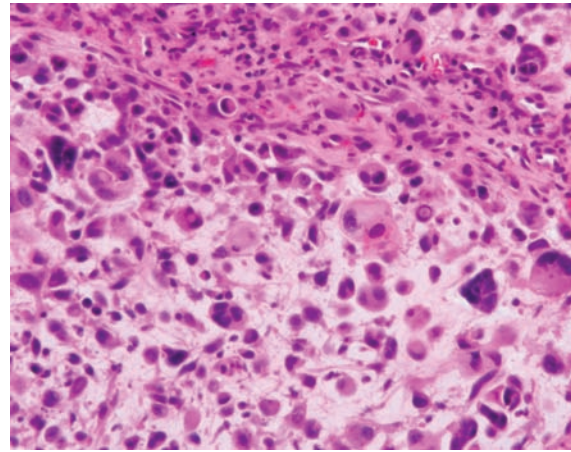
- Poorly differentiated carcinoma
- Large cell lymphoma and plasmacytoma



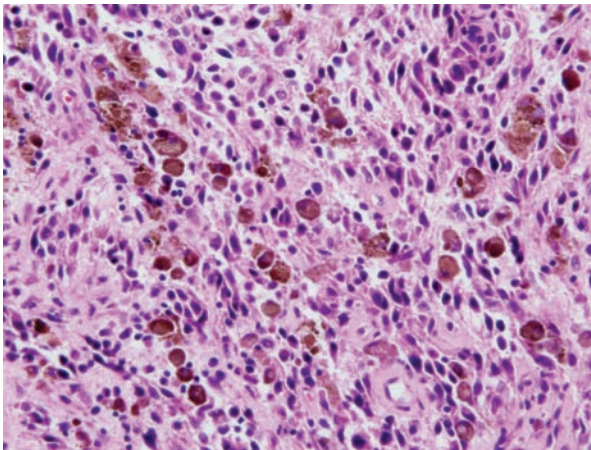
## Mucosal Malignant Melanoma



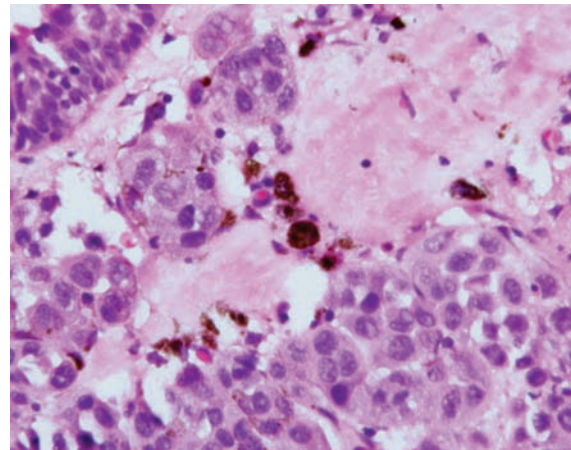
A



B



C



D

**FIGURE 2-13** *Mucosal Malignant Melanoma*

**A.** Spindle cell melanoma can mimic a sarcoma. **B.** Anaplastic variant of melanoma with large pleomorphic multinucleated tumor cells. **C.** Melanin deposits exist primarily in macrophages and melanoma cells are small, imitating a small cell lymphoma. **D.** Epithelioid melanoma cells lie just below nasal mucosa (*upper left*).

### Rhabdomyosarcoma (RMS)

#### DEFINITION:

Primitive malignant small round cell neoplasm showing evidence of skeletal muscle differentiation. Two major histopathologic subtypes include embryonal and alveolar variants with the former more common in children and the latter in adults. Alveolar subtype is associated with a specific genetic translocation, t(2;13)(q35;q14).

#### CLINICAL FEATURES:

- Peak age: adolescents and young adults, may be seen in older adults, but rare in young children
- No gender predilection
- Most common site: parameningeal (paranasal sinus, nasopharynx, periorbital), middle ear
- Nonspecific symptoms include headache, epistaxis, sinusitis, facial swelling, ear pain

#### GROSS AND HISTOLOGIC FINDINGS:

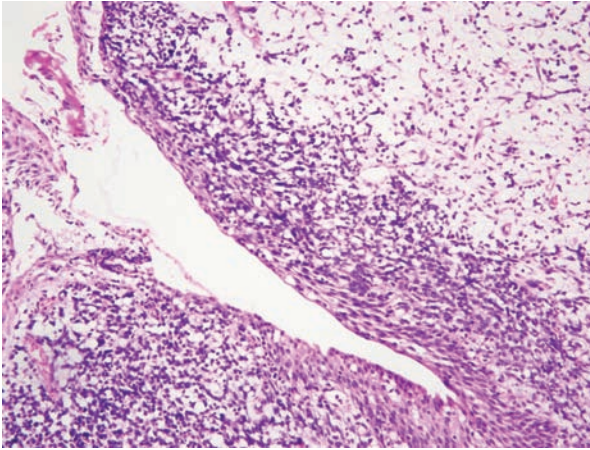
- Gross: off-white mass, botryoid variant of embryonal RMS often polypoid
- Embryonal RMS: malignant “small” cells in a variably myxoid stroma. Botryoid change shows a hypercellular submucosal zone (“cambium layer”) of primitive round and spindle cells with a subjacent edematous stroma. Primitive myofibers show nuclei arranged linearly (**Figure 2-14**)
- Alveolar RMS: sheets of malignant “small” cells variably separated by fibrovascular septa into a loosely cohesive pseudoalveolar pattern; some examples lack this fibrous tissue and are termed “solid variant” of alveolar rhabdomyosarcoma. Cells near the center of these loose alveolar nests may show evidence of rhabdomyomatous differentiation with small amounts of eosinophilic cytoplasm; cytoplasmic cross-striations rare (**Figure 2-15**)
- Rhabdomyoblasts about 3 times the diameter of a resting lymphocyte with hyperchromatic rounded nuclei, indistinct nucleoli; rhabdomyomatous differentiation demonstrated by increasing amounts of eosinophilic cytoplasm
- Positive IHC: myogenin, MyoD1, myoglobin, desmin, PAX-5 (alveolar variant only)
- Alveolar subtype: positive t(2;13)(q35;q14) detected by conventional cytogenetics or FISH

#### DIFFERENTIAL DIAGNOSIS:

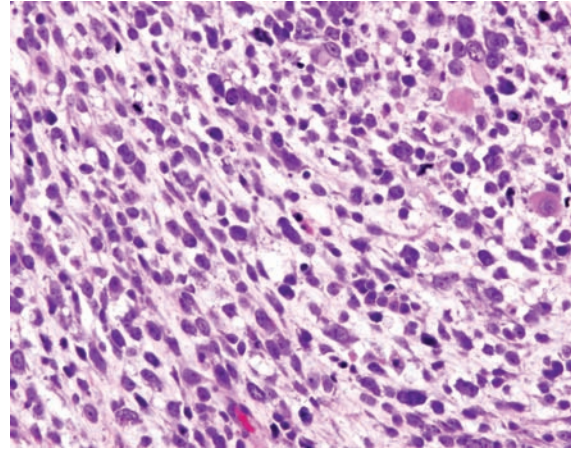
- Non-Hodgkin lymphoma
- Olfactory neuroblastoma
- Sinonasal undifferentiated carcinoma
- Ewing sarcoma
- Small cell neuroendocrine carcinoma



## Rhabdomyosarcoma (RMS)



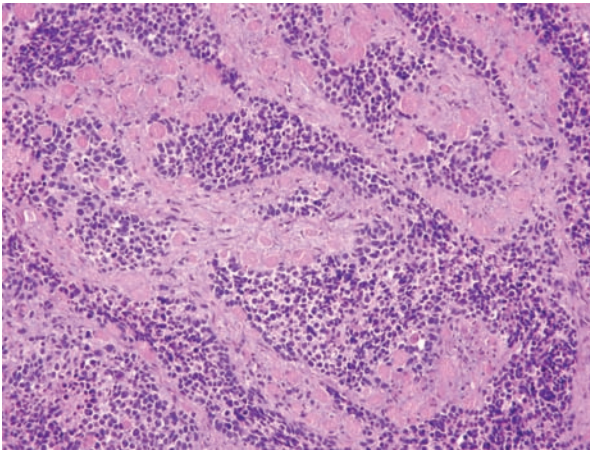
A



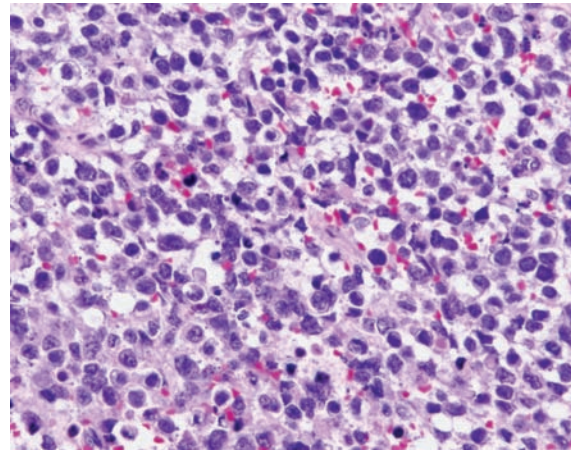
B

**FIGURE 2-14** *Embryonal Rhabdomyosarcoma*

**A.** A hypercellular zone (“cambium layer”) is immediately subjacent to the mucosal surface. **B.** Focal rhabdomyomatous differentiation is characterized by the acquisition of eosinophilic cytoplasm (*right*).



A



B

**FIGURE 2-15** *Alveolar Rhabdomyosarcoma*

**A.** Vague pseudoalveolar nests are formed by fibrous septa. **B.** Primitive rhabdomyoblasts show no convincing rhabdomyomatous differentiation; individual cell necrosis is common.





## Oro/Hypopharynx/Larynx

### **NONNEOPLASTIC LESIONS**

CONTACT ULCER

VOCAL CORD POLYP/NODULES

LARYNGEAL CYSTS

HYPERPLASTIC ALTERATIONS OF THE MUCOSA

### **BENIGN NEOPLASMS**

SQUAMOUS PAPILLOMA

INFLAMMATORY MYOFIBROBLASTIC TUMOR

### **MALIGNANT NEOPLASMS**

BASALOID SQUAMOUS CELL CARCINOMA

VERRUCOUS CARCINOMA

SPINDLE CELL SQUAMOUS CARCINOMA (LANE TUMOR)

PAPILLARY SQUAMOUS CELL CARCINOMA

SMALL CELL NEUROENDOCRINE CARCINOMA

MODERATELY DIFFERENTIATED NEUROENDOCRINE  
CARCINOMA

LARYNGEAL CHONDROSARCOMA

### Contact Ulcer

#### DEFINITION:

Polypoid nodules of ulcerated granulation tissue occurring on one or both true vocal cords as a consequence of various insults to the mucosa, including postintubation trauma, vocal abuse, and gastroesophageal reflux.

#### CLINICAL FEATURES:

- Broad age range: men affected slightly more than women
- Nonspecific symptoms include hoarseness, sore throat, and dysphonia
- Most common at the posterior portion of the true vocal cord

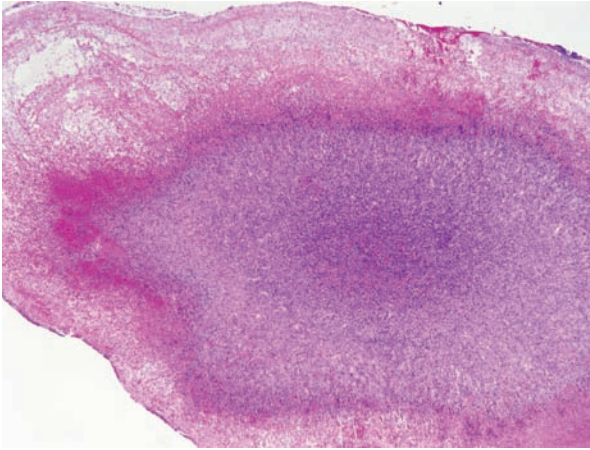
#### GROSS AND HISTOLOGIC FINDINGS:

- Gross: polypoid, focally ulcerated tan-white to erythematous mass
- Ulcerated mucosa with fibrinopurulent superficial layer overlies small capillaries oriented perpendicularly to the mucosal surface and a dense inflammatory infiltrate and proliferating fibroblasts (**Figure 3-1**)
- Chronic cases are associated with mucosal hyperplasia

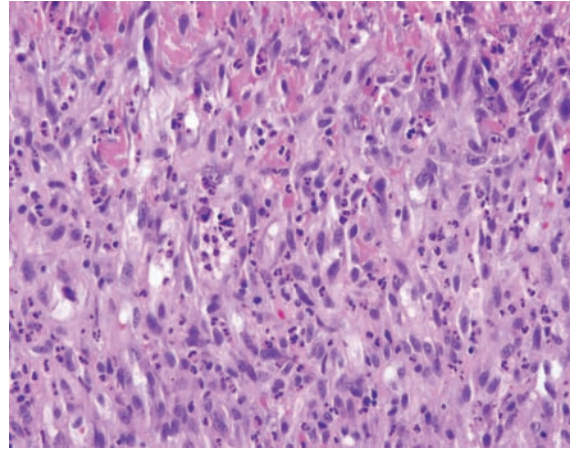
#### DIFFERENTIAL DIAGNOSIS:

- Hemangioma
- Vocal cord polyp

### Contact Ulcer



A



B

**FIGURE 3-1** *Contact Ulcer*

**A.** A thick layer of ulcerated edematous fibrinopurulent material coats the surface of this nodule. **B.** Granulation tissue underlying the fibrinous ulcer contains a mixture of proliferating fibroblasts, small capillaries, and neutrophils.

### Vocal Cord Polyp/Nodules

#### DEFINITION:

Reactive, nonneoplastic polypoid lesion(s) of the vocal cord typically as a consequence of chronic voice abuse. By convention, the term vocal cord “nodule” is used for bilateral lesions, and “polyp” for a unilateral one.

#### CLINICAL FEATURES:

- Nodules are more common in children and young adults; slight predominance in women
- Most occur in the middle third of the true cord
- Nonspecific symptoms include hoarseness, sore throat, and change in phonation

#### GROSS AND HISTOLOGIC FINDINGS:

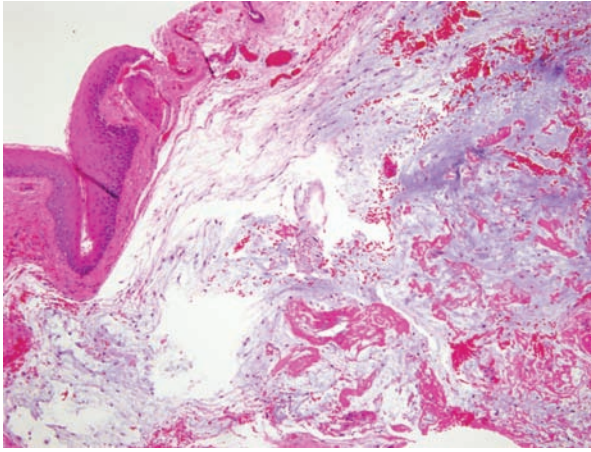
- Gross: sessile nodule ranging from polypoid to fusiform, off-white to bright red, and varies from firm to mucoid and glistening
- Historically divided into four histologic subtypes (myxoid, fibrous, hyaline, and vascular) that often have mixed features of more than one type; these have no biologic relevance
- Myxoid subtype: hypocellular myxoid stroma; fibrous subtype: oval and spindle cells embedded in a variably fibrous stroma; hyaline subtype: deeply eosinophilic hypocellular/acellular stroma; vascular subtype: ectatically dilated vascular channels with hypocellular stroma (**Figure 3-2**)
- Overlying mucosa is normal, atrophic, or hyperplastic with or without keratosis

#### DIFFERENTIAL DIAGNOSIS:

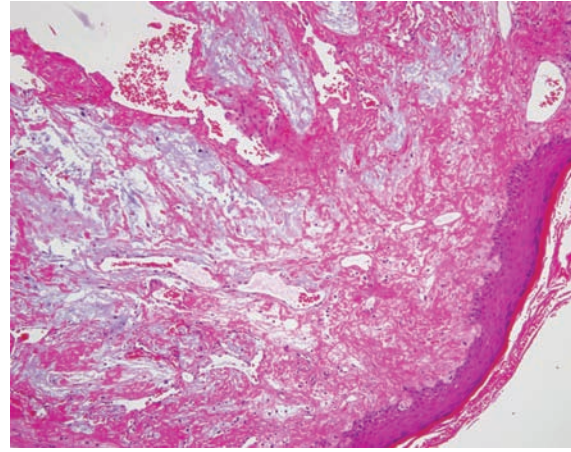
- Hyaline type: amyloidosis



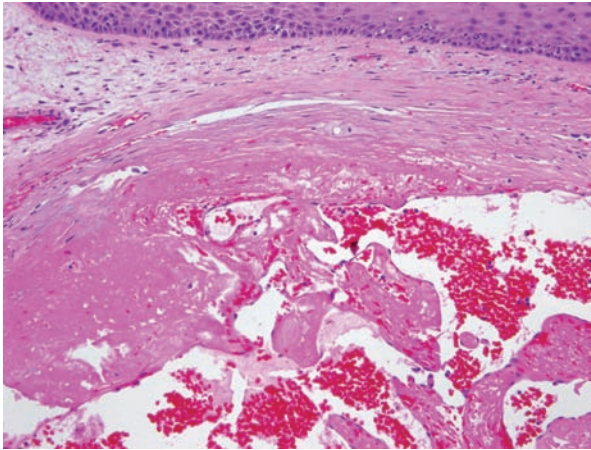
## Vocal Cord Polyp/Nodules



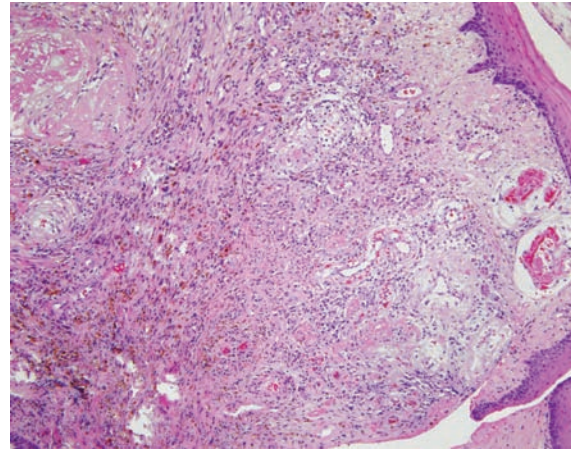
A



B



C



D

**FIGURE 3-2** *Vocal Cord Polyps*

**A.** Myxoid variant. **B.** Mixed myxoid-hyaline subtype. Note the mucosal keratosis.  
**C.** Vascular subtype. **D.** Fibrous subtype. Hemosiderin deposition is present.

### Laryngeal Cysts

#### DEFINITION:

Laryngocele is an abnormal cystic dilatation of the laryngeal saccule maintaining an open communication with laryngeal lumen. An oncocytic cyst occurs in the false cord and is lined by oncocytic epithelium. A saccular cyst is similar to laryngocele but is closed with no communication into the larynx. Nonspecific epithelial cysts may occur in the vallecula, supraglottis, and pyriform sinus.

#### CLINICAL FEATURES:

- Occur in all age groups
- Nonspecific symptoms include hoarseness, globus sensation, persistent cough, and dysphagia

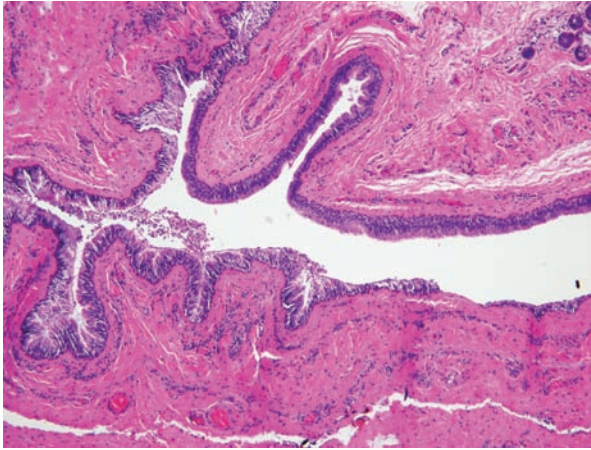
#### GROSS AND HISTOLOGIC FINDINGS:

- Gross: typically received as a soft, often collapsed cyst with variable amount of thick mucus or serous fluid
- All cysts lined by benign epithelium that varies from ciliated respiratory type to squamous to oncocytic and has a fibrous wall of variable thickness. Oncocytic cysts with proliferating papillary infoldings are termed oncocytic cystadenoma (**Figure 3-3**)
- Variable amount of inflammation may surround cysts
- IHC: not helpful

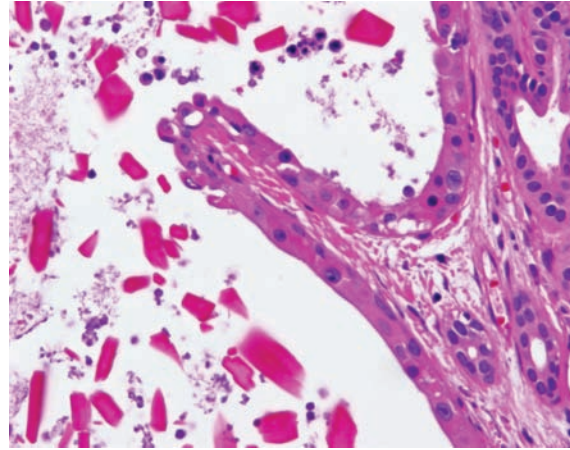
#### DIFFERENTIAL DIAGNOSIS:

- Cystic squamous carcinoma
- Clinically may resemble a prolapsed laryngeal ventricular fold

## Laryngeal Cysts



A



B

**FIGURE 3-3** *Laryngeal Cysts*

**A.** Collapsed laryngocele has an empty lumen and is lined by ciliated respiratory-type epithelium. **B.** Oncocytic cystadenoma shows papillary infolding and a simple cuboidal epithelium with oncocytic metaplasia. Intensely eosinophilic crystalloids are present in the lumen.

### Hyperplastic Alterations of the Mucosa

#### DEFINITION:

Reparative process resulting from a variety of injurious stimuli leading to an increased thickness of the squamous mucosa and its covering with no biologic precancerous risk. The section on epithelial precancerous lesions is in Chapter 1.

#### CLINICAL FEATURES:

- Primarily affects true and false cords in adults with a slight predilection for men
- Nonspecific symptoms include hoarseness, chronic nonproductive cough, changes in phonation
- Associated with heavy tobacco use, alcohol use, and voice abuse

#### GROSS AND HISTOLOGIC FINDINGS:

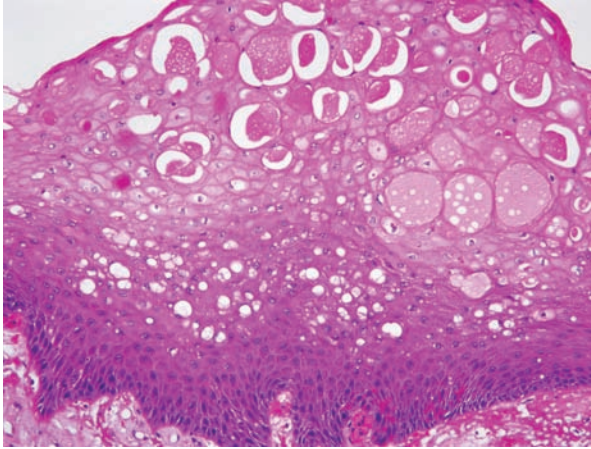
- Gross: verrucous, flat, or slightly papillary; white (leukoplakia) or reddish (erythroplakia) plaque-like foci, often without sharp borders
- Microscopic alterations include eosinophilic pooling (pools of PAS-positive proteinaceous material within the superficial mucosa of no biologic significance), keratosis (a keratin layer overlying the squamous mucosa without nuclei or with nuclei (parakeratosis)), increased thickness of the spinous layer of squamous mucosa (squamous hyperplasia), radiation-induced atypia (enlarged cell nuclei often smudged but no appreciable increase in N/C ratio), and downward growth of elongated finger-like or bulbous projections of nondysplastic rete pegs extending into the stroma (pseudoepitheliomatous hyperplasia) (**Figure 3-4**)

#### DIFFERENTIAL DIAGNOSIS:

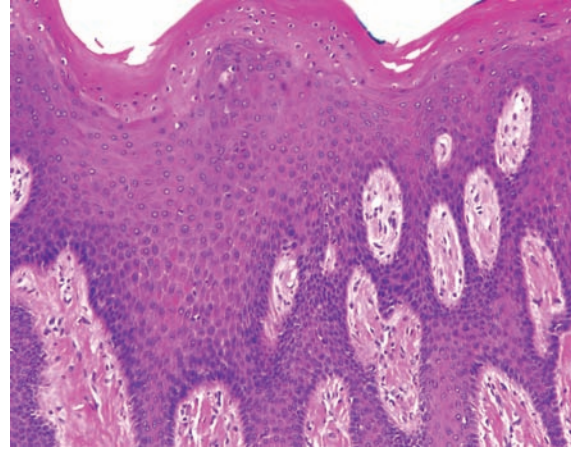
- Well-differentiated squamous cell carcinoma
- Epithelial dysplasia



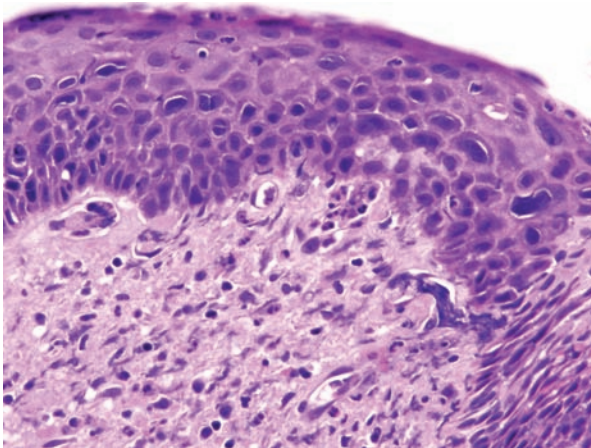
## Hyperplastic Alterations of the Mucosa



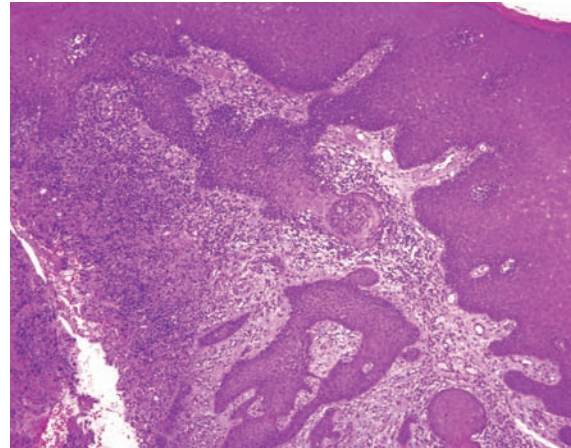
A



B



C



D

**FIGURE 3-4** *Hyperplastic Alterations of the Mucosa*

**A. Eosinophilic pooling.** This pseudohyperplastic phenomenon consists of plasma originating from underlying stroma that leads to pools of homogeneous/granular material within the superficial epithelium. **B. Keratosis/parakeratosis.** A keratin layer containing pyknotic nuclei (parakeratosis) is present on the laryngeal surface. The tangential section makes it look as though squamous hyperplasia is present. **C. Radiation-induced atypia.** Metaplastic squamous epithelium from the supraglottis shows isolated enlarged, misshapen, and hyperchromatic nuclei. **D. Pseudoepitheliomatous hyperplasia.** Hyperplastic laryngeal mucosa shows surface keratosis and irregularly configured seemingly detached islands of benign squamous epithelium in the submucosa resembling invasive squamous carcinoma.



### Squamous Papilloma

#### DEFINITION:

Benign exophytic epithelial neoplasm, single or multiple, composed of rounded papillary protrusions and caused by HPV infection.

#### CLINICAL FEATURES:

- Two clinical types: adult type (usually single, less likely to recur), juvenile type (typically multiple lesions with a marked tendency to recur and become aggressive). In addition to the larynx, the juvenile type may involve the entire tracheobronchial tree and is associated with airway obstruction and increased mortality
- Adult type: decades 3 to 4; juvenile type: <10 years old
- May involve both true and false vocal cords with possible extension to subglottis, and tracheobronchial tree
- Symptoms include hoarseness, chronic cough, stridor, change in phonation
- Most often associated with human papilloma virus HPV-11 and HPV-6

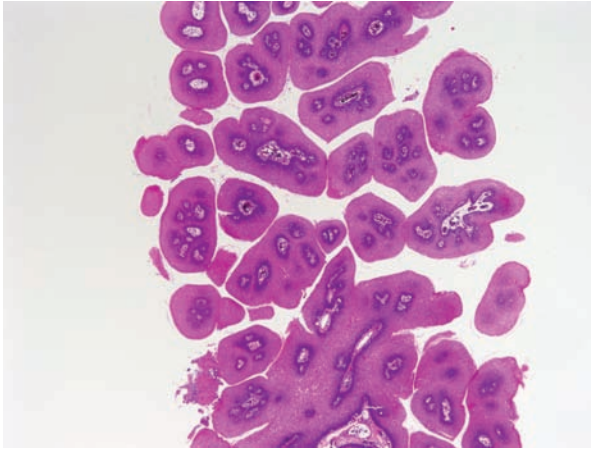
#### GROSS AND HISTOLOGIC FINDINGS:

- Gross: exophytic pedunculated or sessile papillary tan-white mass(es)
- Multiple finger-like branching projections contain thin fibrovascular cores covered by smooth-surfaced squamous mucosa that shows parabasal hyperplasia, occasional koilocytosis (more common in juvenile type) and dyskeratosis with variable (usually minimal) keratosis/parakeratosis (**Figure 3-5**)
- Most examples will not demonstrate epithelial dysplasia
- Positive in situ hybridization: HPV

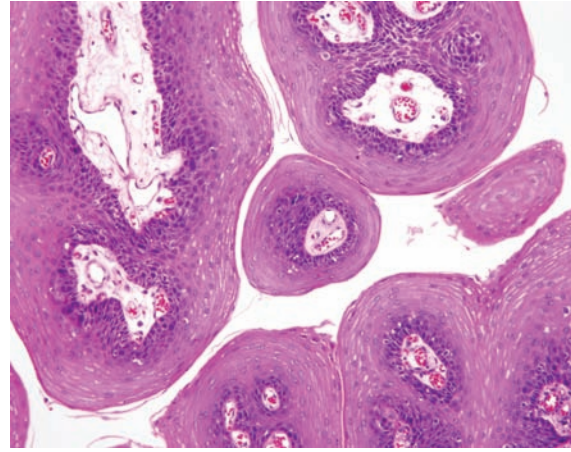
#### DIFFERENTIAL DIAGNOSIS:

- Papillary squamous cell carcinoma
- Verrucous squamous cell carcinoma

## Squamous Papilloma



A



B

**FIGURE 3-5** *Squamous Papilloma*

**A.** Detached papillary fronds of multilayered nondysplastic squamous epithelium lack a keratin layer. **B.** Squamous cells have a low N/C ratio and show a normal maturation from basal to surface layers.

### Inflammatory Myofibroblastic Tumor

#### DEFINITION:

Low-grade neoplastic mass-forming proliferation of spindle cells having morphologic and immunohistologic features of myofibroblasts and accompanied by an inflammatory infiltrate composed of lymphocytes, plasma cells, and eosinophils.

#### CLINICAL FEATURES:

- Adults
- Larynx is most common head and neck site, but still rare in head and neck; also seen in oral cavity, paranasal sinuses
- Nonspecific symptoms include hoarseness, dyspnea, stridor

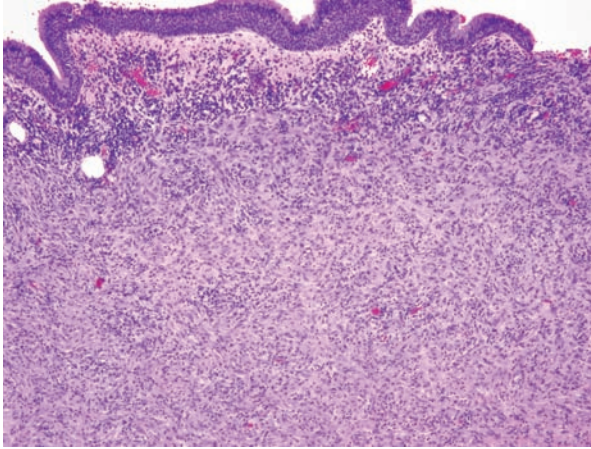
#### GROSS AND HISTOLOGIC FINDINGS:

- Gross: exophytic polypoid sessile or pedunculated mass
- Submucosal increase in spindle and stellate myofibroblastic cells with banal nuclei arranged in abortive fascicles and loose storiform pattern in an edematous or myxoid stroma, and numerous plasma cells with lesser number of lymphocytes, and eosinophils (**Figure 3-6**)
- Low mitotic activity; absence of atypical mitoses
- Positive IHC: vimentin, smooth muscle actin, muscle specific actin; focal cytokeratin staining in up to 60% of cases. ALK-1 stain typically negative in head and neck

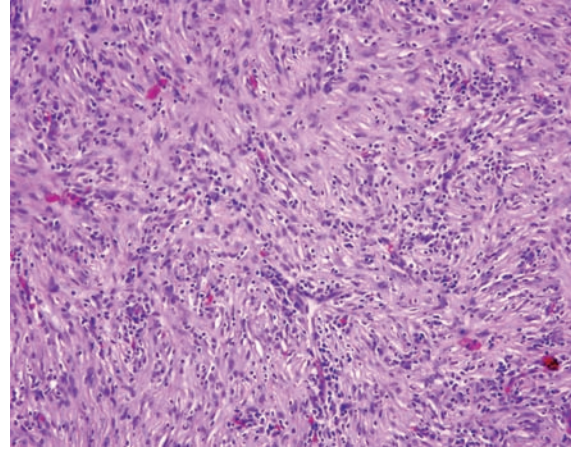
#### DIFFERENTIAL DIAGNOSIS:

- Exuberant granulation tissue
- Spindle cell carcinoma
- Spindle cell sarcomas

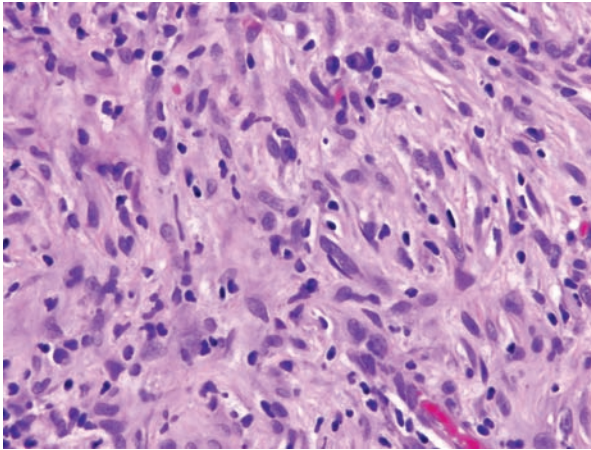
## Inflammatory Myofibroblastic Tumor



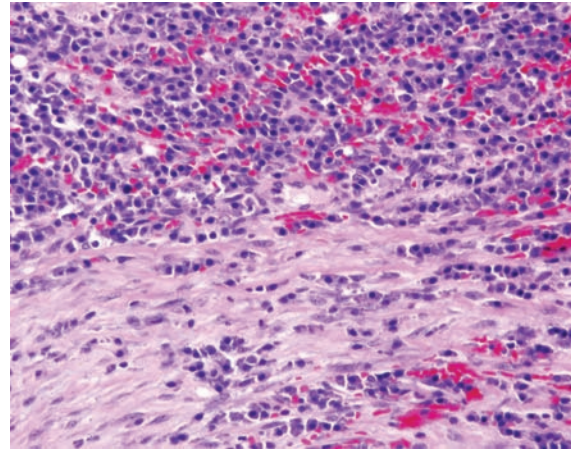
A



B



C



D

**FIGURE 3-6** *Inflammatory Myofibroblastic Tumor*

**A.** A small zone separates the spindle cell proliferation from the mucosal surface. **B.** Spindle cells generate a vague storiform pattern and are mixed with a sparse lymphoplasmacytic infiltrate. **C.** Spindle cell nuclei are euchromatic with small barely perceptible nucleoli. **D.** Focus containing a dense plasmacytic infiltrate.

### Basaloid Squamous Cell Carcinoma

#### DEFINITION:

Squamous carcinoma composed of a dominant population of malignant basaloid cells usually in association with conventional invasive or in situ squamous carcinoma.

#### CLINICAL FEATURES:

- Elderly men more commonly affected
- Hypopharynx most common site; also supraglottic larynx, oral cavity, oropharynx
- Symptoms include hoarseness, voice change, neck pain, and neck mass
- Oropharyngeal carcinoma associated with HPV infection, younger age, history of oral sex, much better prognosis
- Tobacco and alcohol abuse are contributing factors

#### GROSS AND HISTOLOGIC FINDINGS:

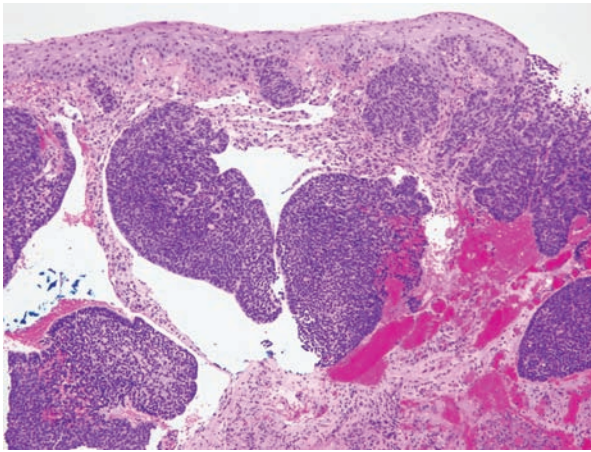
- Gross: primarily endophytic firm, off-white masses with necrosis
- Patterns include cribriform, solid, trabecular, and lobular forms populated by a relatively monotonous population of closely packed smaller cells with minimal cytoplasm, hyperchromatic nuclei—many with indistinct nucleoli, and numerous mitoses (**Figure 3-7**)
- Central comedo-type necrosis common, as is peripheral palisading of nuclei surrounding lobules
- Conventional squamous carcinoma is a minor feature; may consist of only surface epithelial dysplasia or focal individual cell keratinization
- Stroma often hyalinized
- Positive IHC: p63, high-molecular-weight cytokeratin (34 $\beta$ E12); positive p16 and high-risk HPV by ISH or PCR (oropharynx in particular); negative for neuroendocrine, myogenic, and melanoma markers

#### DIFFERENTIAL DIAGNOSIS:

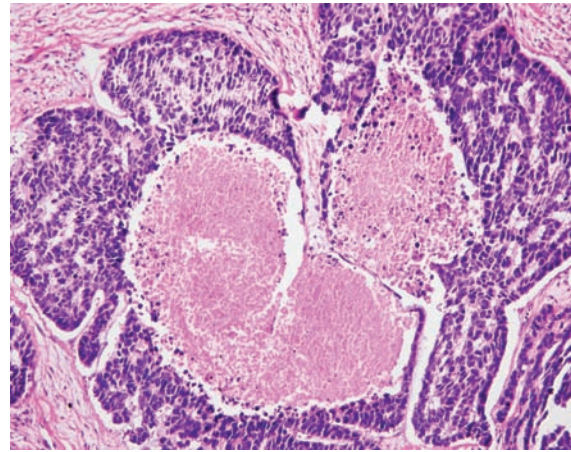
- Small cell neuroendocrine carcinoma
- Adenoid cystic carcinoma
- Non-Hodgkin lymphoma



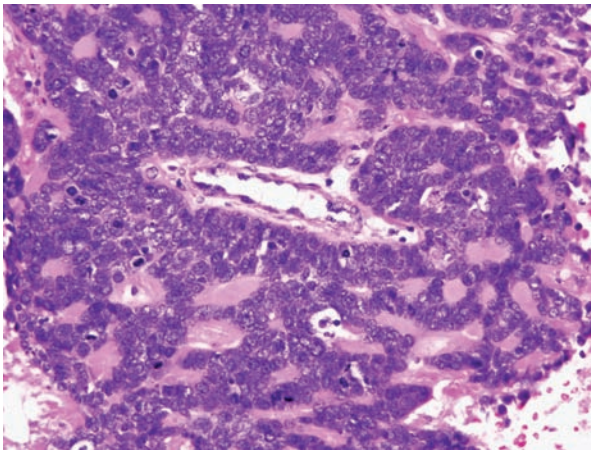
## Basaloid Squamous Cell Carcinoma



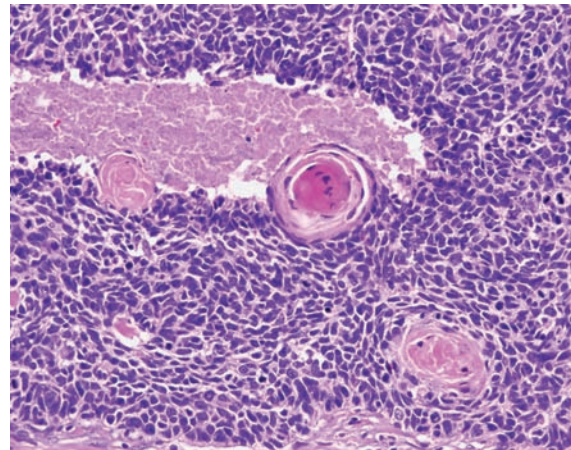
A



B



C



D

**FIGURE 3-7** *Basaloid Squamous Cell Carcinoma*

**A.** Nests of carcinoma emanate from the mucosal surface. **B.** Lobular nests display central comedo-type necrosis. Note the adenoid pattern surrounding the necrotic center.

**C.** Stromal hyalinosis mimics the cribriform pattern of adenoid cystic carcinoma.

**D.** Abrupt focus of keratinizing squamous differentiation is set in a solid sheet of malignant basaloid cells.

### Verrucous Carcinoma

#### DEFINITION:

Nonmetastatic squamous carcinoma composed of well-differentiated epithelium and characterized by wart-like exophytic growth and smooth “pushing” margins. This histopathologic diagnosis cannot be made with superficial biopsies.

#### CLINICAL FEATURES:

- Elderly men most commonly affected
- Oral cavity, larynx, and sinonasal tract are common sites
- Laryngeal involvement is most often localized to the true vocal cord
- Symptoms include hoarseness, globus sensation

#### GROSS AND HISTOLOGIC FINDINGS:

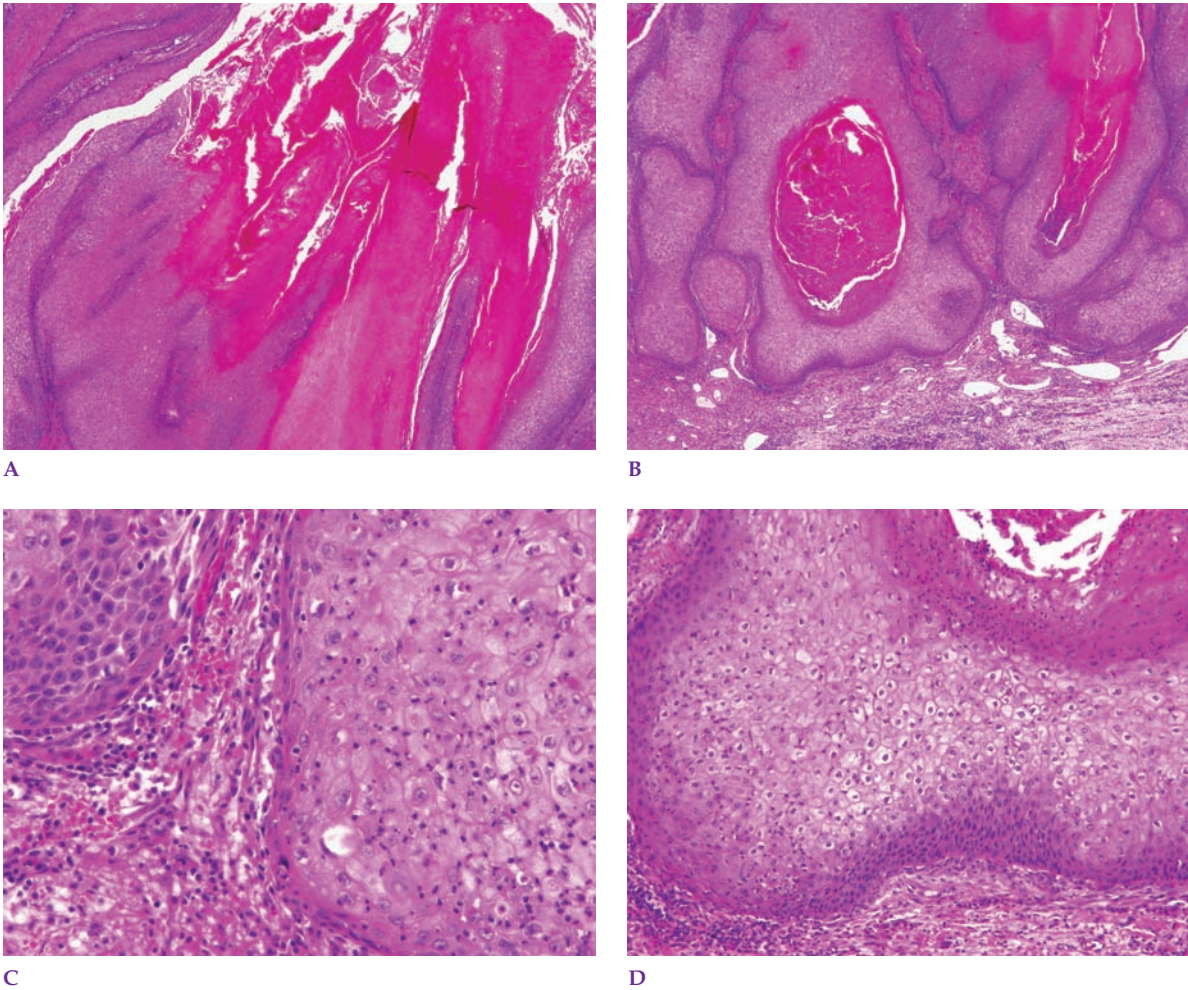
- Gross: off-white, sessile warty lesion
- Squamous epithelium is hyperplastic, extremely well-differentiated lacking cytologic atypia and mitoses with verrucoid spires of surface keratinization, broad rete pegs and a noninfiltrative border (**Figure 3-8**)
- Distinction from verrucous hyperplasia often subjective with carcinoma typically showing deep extensions into underlying fibrous tissue
- Mixed inflammatory infiltrate hugs the stromal—mucosal interface

#### DIFFERENTIAL DIAGNOSIS:

- Verrucous hyperplasia
- Well-differentiated squamous cell carcinoma
- Verruca vulgaris



## Verrucous Carcinoma



**FIGURE 3-8** *Verrucous Carcinoma*

**A.** Elongated spikes of squamous epithelium with multiple keratin layers characterize the top half of this carcinoma. **B.** Smooth bulbous rete pegs characterize the bottom half of the same hyperplastic epithelium. Large masses of keratin are present.

**C.** High magnification emphasizes the smooth rounded edges of the neoplasm, the banal cytomorphology, and a brisk neutrophilic infiltrate. **D.** Focal cytoplasmic clearing is encountered.

### Spindle Cell Squamous Carcinoma (Lane Tumor)

#### DEFINITION:

Squamous carcinoma composed of a dominant population of malignant spindle cells coupled with an in situ or invasive conventional squamous carcinoma. The spindle cell component is epithelial in nature.

#### CLINICAL FEATURES:

- Decades 5 to 7 with strong male predominance; history of radiation in a minority of cases
- Larynx (true vocal cord) is the most common site followed by oral cavity
- Nonspecific symptoms include hoarseness, dysphagia, globus sensation, voice change, hemoptysis

#### GROSS AND HISTOLOGIC FINDINGS:

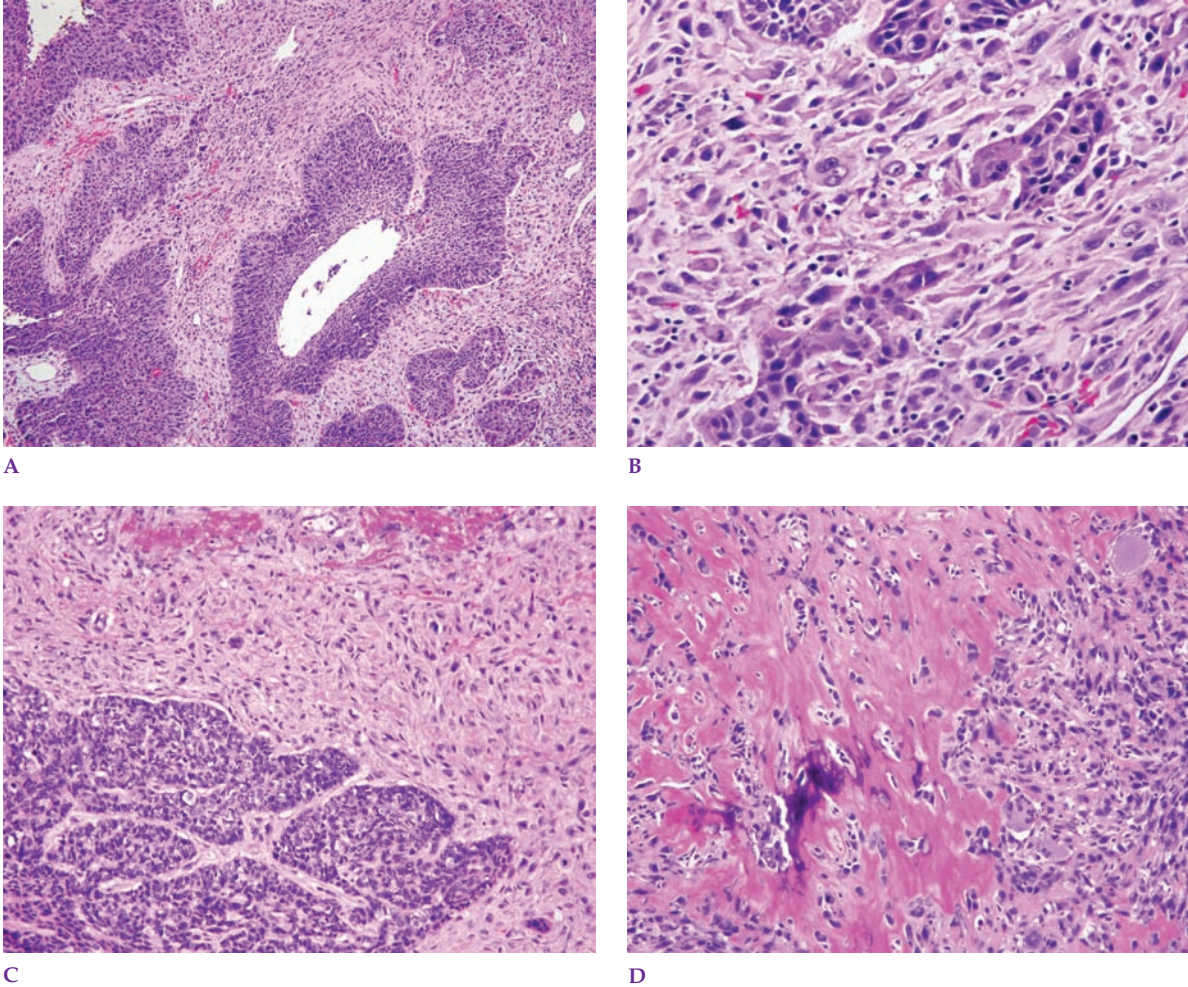
- Gross: polypoid, exophytic mass; small proportion are ulcerated and infiltrative
- Mostly a biphasic neoplasm with foci of carcinoma intimately associated with a malignant spindle cell proliferation showing a variety of patterns including storiform, fascicular and herringbone; up to one-third of cases are monophasic spindle cell neoplasms
- Spindle cell component shows marked hypercellularity with cells having bland, large, pleomorphic or hyperchromatic nuclei, enlarged nucleoli, and obvious (frequently atypical) mitoses (**Figure 3-9**)
- Collagenized variant: hypocellular malignancy with pleomorphic cells scattered in a fibrous stroma
- Heterologous osseous, cartilaginous, or skeletal muscle differentiation are possible
- Surface carcinoma in situ often present
- Metastases may demonstrate conventional and spindle cell squamous carcinoma combined or either one separately
- Positive IHC: vimentin, p63 (50%), pan-cytokeratin, EMA; negative cytokeratin staining and other epithelial markers in up to one-third of cases
- Spindle cell malignancy in this site is more apt to be spindle cell (sarcomatoid) carcinoma rather than a sarcoma even if keratin stains are negative

#### DIFFERENTIAL DIAGNOSIS:

- Spindle cell sarcomas of various types
- Spindle cell melanoma
- Inflammatory myofibroblastic tumor
- Exuberant granulation tissue



## Spindle Cell Squamous Carcinoma (Lane Tumor)



**FIGURE 3-9** *Spindle Cell Carcinoma*

**A.** Biphasic example shows islands of poorly differentiated squamous carcinoma set in a sarcomatoid stroma. **B.** Nuclear pleomorphism and multinucleation are obvious. **C.** Basaloid carcinoma comprises the nonsarcomatoid component in this example. **D.** Heterologous osteosarcomatous differentiation is present.



### Papillary Squamous Cell Carcinoma

#### DEFINITION:

Squamous carcinoma characterized by an obvious exophytic papillary growth pattern that comprises the bulk of the neoplasm.

#### CLINICAL FEATURES:

- Elderly men most often affected
- Larynx and hypopharynx are the most common sites
- Symptoms include hemoptysis, hoarseness, sore throat

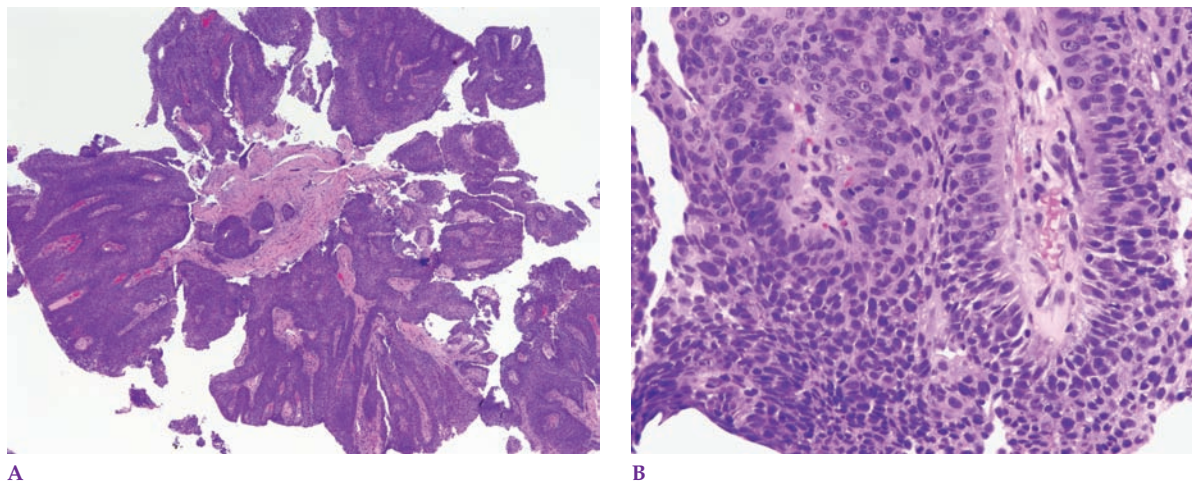
#### GROSS AND HISTOLOGIC FINDINGS:

- Gross: polypoid, papillary mass that is often friable that may or may not have a stalk
- Exophytic smooth-surfaced finger-like papillary fronds have central fibrovascular cores or broad bulbous projections and are covered by cytologically malignant predominantly nonkeratinizing mucosa that is similar to squamous carcinoma in situ (**Figure 3-10**)
- Invasive component may be absent and is often missing in biopsy specimens
- Positive IHC: if oropharyngeal location likely positive for p16, high-risk HPV (in situ hybridization)

#### DIFFERENTIAL DIAGNOSIS:

- Squamous papilloma
- Conventional squamous cell carcinoma

## Papillary Squamous Cell Carcinoma



**FIGURE 3-10** *Papillary Squamous Cell Carcinoma*

**A.** Detached papillary fragments are common; invasion cannot be assessed.

**B.** The mucosa shows full thickness carcinoma.

### Small Cell Neuroendocrine Carcinoma

#### DEFINITION:

High-grade chemosensitive carcinoma composed of “small” cells with minimal visible cytoplasm, high-mitotic count, necrosis, and immunohistochemical evidence of neuroendocrine differentiation.

#### CLINICAL FEATURES:

- Rare as a laryngeal primary; middle-age to elderly individuals; male predominance
- Symptoms include dysphagia, dysphonia, and hemoptysis
- Strong association with heavy smokers
- Supraglottis is most common site

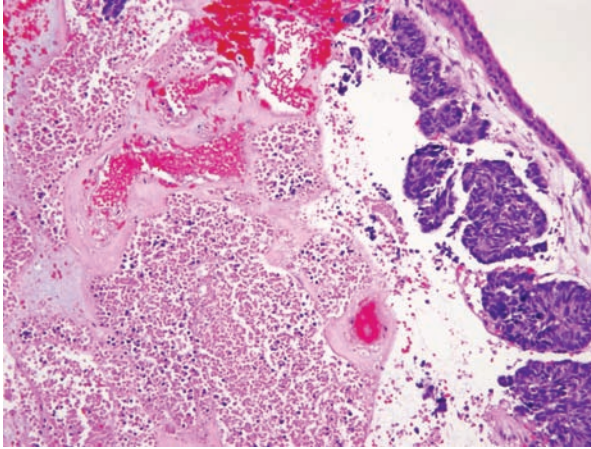
#### GROSS AND HISTOLOGIC FINDINGS:

- Gross: ulcerated, off-white mass
- Hypercellular solid sheets, ribbons, and nests of cells; cells are three times the diameter of a resting lymphocyte with markedly hyperchromatic rounded, oval and fusiform nuclei and barely visible cytoplasm; nuclei are characterized by an absence of discrete nucleoli, “molding” into one another and chromatin coarseness (**Figure 3-11**)
- Individual cell necrosis, geographic necrosis, high-mitotic activity, perineural invasion, and “crush” artifact are the rule
- Absence of squamous differentiation
- Positive IHC: pan-cytokeratin, CD56, synaptophysin, TTF-1, chromogranin (variable); negative for p63, high-molecular-weight cytokeratin (34 $\beta$ E12), S-100

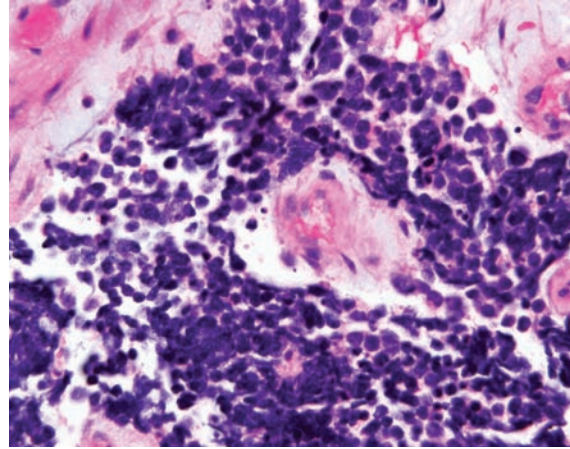
#### DIFFERENTIAL DIAGNOSIS:

- Basaloid squamous cell carcinoma
- Lymphoma
- Malignant melanoma
- Solid variant of adenoid cystic carcinoma

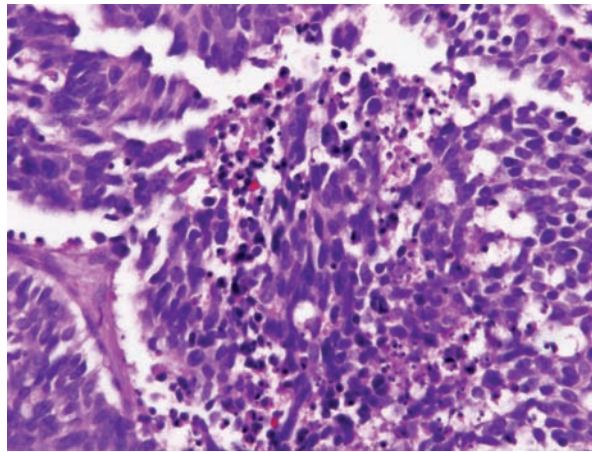
## Small Cell Neuroendocrine Carcinoma



A



B



C

**FIGURE 3-11** *Small Cell Neuroendocrine Carcinoma*

**A.** Nests of carcinoma are directly subjacent to the laryngeal mucosa. Abundant geographic necrosis is seen below these nests. **B.** Hyperchromatic nuclei mold with each other and show chromatin smearing. **C.** Both rounded and fusiform shapes are seen with scattered individual cell ("mercury-droplet" type) necrosis.

### Moderately Differentiated Neuroendocrine Carcinoma

#### DEFINITION:

Intermediate-high-grade carcinoma with immunohistochemical evidence of neuroendocrine differentiation, and composed of cells with moderate to abundant cytoplasm, but fewer mitoses, and less necrosis than small cell neuroendocrine carcinoma.

#### CLINICAL FEATURES:

- Most common neuroendocrine neoplasm of larynx
- Association with heavy smokers
- Supraglottis is most common site

#### GROSS AND HISTOLOGIC FINDINGS:

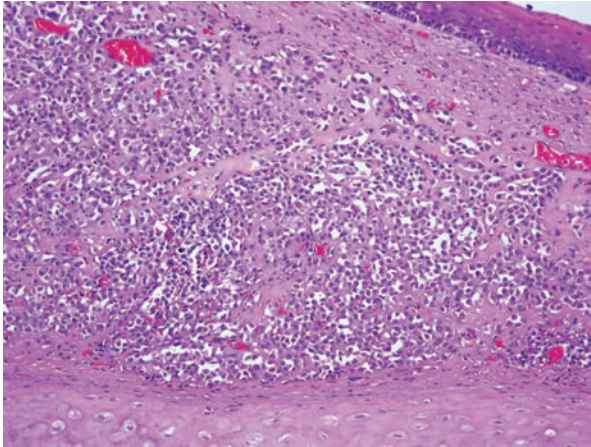
- Gross: off-white polypoid mass, typically submucosal
- Hypercellular with vague to well-developed patterns of growth including organoid, trabecular, and solid architecture
- Cells have round to oval nuclei, variable presence and size of nucleoli, coarse chromatin, and a moderate amount of eosinophilic cytoplasm (**Figure 3-12**)
- Scattered mitoses, punctate foci of necrosis
- Positive IHC: pan-cytokeratin, CD56, synaptophysin, chromogranin, CEA, calcitonin; negative for p63, high-molecular-weight cytokeratin (34 $\beta$ E12), S-100, TTF-1, HMB45

#### DIFFERENTIAL DIAGNOSIS:

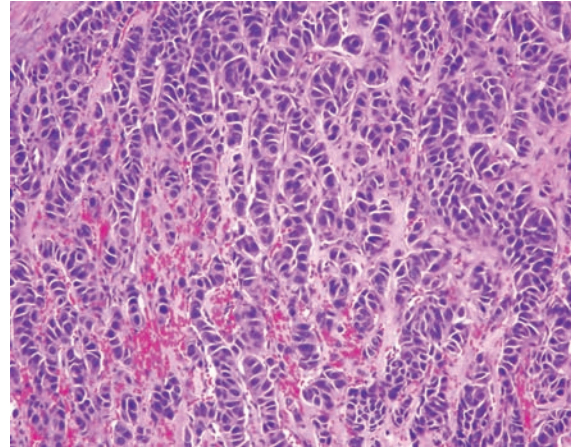
- Well-differentiated neuroendocrine carcinoma (carcinoid tumor)
- Medullary thyroid carcinoma
- Malignant melanoma
- Paraganglioma



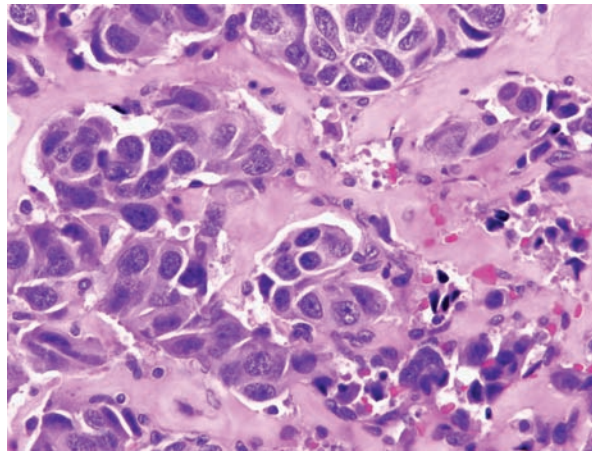
## Moderately Differentiated Neuroendocrine Carcinoma



A



B



C

**FIGURE 3-12** *Moderately Differentiated Neuroendocrine Carcinoma*

**A.** Carcinoma penetrates between the elastic cartilage of the epiglottis (below) and overlying mucosa. **B.** Ribbons of malignant cells show nuclear molding and eosinophilic cytoplasm. **C.** Nuclei have “salt and pepper” chromatin and moderate amount of eosinophilic cytoplasm; some have micronucleoli.

### Laryngeal Chondrosarcoma

#### DEFINITION:

Malignant cartilaginous neoplasm (mostly low-grade) arising in laryngeal cartilage with potential for local recurrence and rarely metastasis.

#### CLINICAL FEATURES:

- Nonspecific symptoms include neck mass, hoarseness, dysphagia, and dyspnea
- Decades 4 to 8; M:F about 4:1
- Plain X-rays: fine to coarse calcification within a mass; may show a destructive pattern of infiltration
- Cricoid cartilage affected >> thyroid or arytenoid cartilages

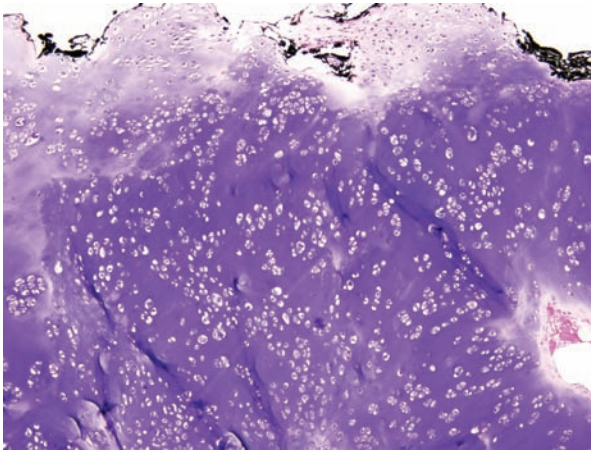
#### GROSS AND HISTOLOGIC FINDINGS:

- Gross: hard, lobular mass with a partially calcified glistening off-white to gray cut surface
- Low-grade chondrosarcoma: a modestly increased number of chondrocytes are set in an abundant blue-gray chondroid matrix usually retaining a clustered lacunar architecture; rounded chondrocyte nuclei show some nuclear enlargement, increased N/C ratio, and binucleation (**Figure 3-13**)
- High-grade chondrosarcoma: a visibly hypercellular neoplasm with single cells showing moderate-marked pleomorphism set in a myxoid rather than chondroid matrix, increased mitoses, and necrosis
- Separation of low-grade chondrosarcoma from chondroma not always possible microscopically; debatable whether laryngeal chondroma exists; most chondrosarcoma are >2 cm
- Positive IHC: S-100, vimentin; negative with pan-keratin antibodies

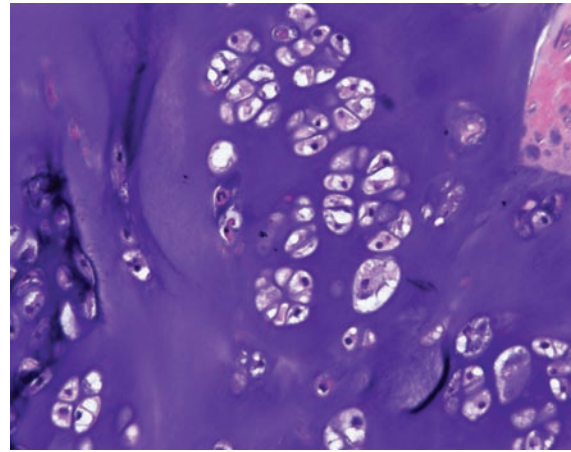
#### DIFFERENTIAL DIAGNOSIS:

- Laryngeal chondroma
- Chondrometaplasia

## Laryngeal Chondrosarcoma



A



B

**FIGURE 3-13** *Laryngeal Chondrosarcoma, Grade I*

**A.** A lobular fragment of cartilaginous tissue contains abundant matrix. **B.** Chondrocyte clusters are in an acinar arrangement and exhibit cytologically atypical features.



## Salivary Gland

### **NONNEOPLASTIC LESIONS**

SIALOLITHIASIS

CHRONIC FIBROSING SIALADENITIS (KUTTNER TUMOR)

LYMPHOEPITHELIAL SIALADENITIS

### **BENIGN NEOPLASMS**

PLEOMORPHIC ADENOMA

WARTHIN TUMOR

BASAL CELL ADENOMA

ONCOCYTOMA

MYOEPITHELIOMA

### **MALIGNANT NEOPLASMS**

MUCOEPIDERMOID CARCINOMA

ACINIC CELL ADENOCARCINOMA (ACC)

ADENOID CYSTIC CARCINOMA (ADCC)

POLYMORPHOUS LOW-GRADE ADENOCARCINOMA

EPITHELIAL-MYOEPITHELIAL CARCINOMA

CLEAR CELL CARCINOMA, NOS

SALIVARY DUCT CARCINOMA

CARCINOMA EX PLEOMORPHIC ADENOMA



### Sialolithiasis

#### DEFINITION:

Existence of a calcific concretion(s) within the salivary duct(s) and/or parenchyma.

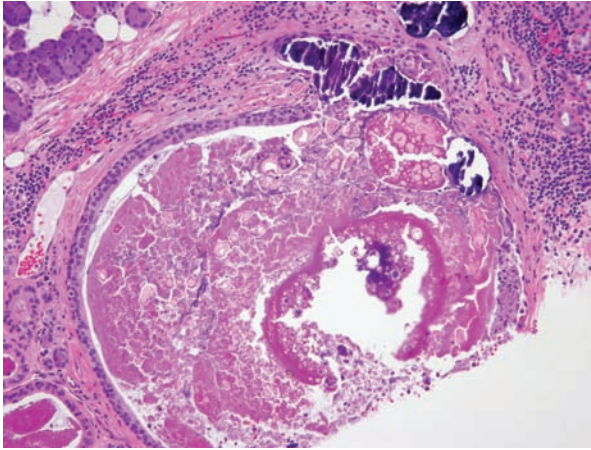
#### CLINICAL FEATURES:

- Middle-aged adults, but broad age range
- Most common in Wharton's duct (submandibular) and less so in Stensen's duct (parotid)
- Pain usually during eating and swelling

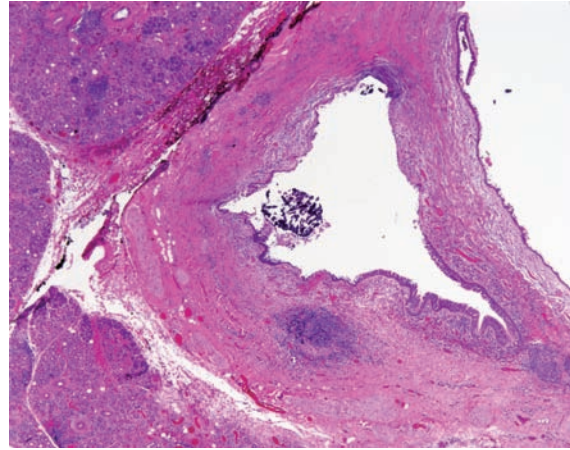
#### GROSS AND HISTOLOGIC FINDINGS:

- Gross: hard yellow-white spherical concretion(s) usually <2 cm in diameter; gland has variable firmness, and cystic change
- Markedly dilated duct contains a laminated calcific nodule; the surrounding duct can have squamous, mucinous, or oncocytic metaplasia
- Calculi may be present also with gland parenchyma; salivary gland shows a fibrosing lymphoplasmacytic sialadenitis, variable ductular dilatation, and in long-standing cases, acinar gland atrophy (**Figure 4-1**)

## Sialolithiasis



A



B

**FIGURE 4-1** *Sialolithiasis*

**A.** Small sialolith is present in the dilated lumen of this small duct. **B.** There is marked ductal dilatation with surrounding fibrosis and chronic inflammation. Only a small fragment of the calculus is present.

### Chronic Fibrosing Sialadenitis (Kuttner Tumor)

#### DEFINITION:

IgG4-related tumor-like inflammatory condition of the salivary glands clinically suspicious for a malignant neoplasm.

#### CLINICAL FEATURES:

- Most patients older than 50 years; slight male predominance
- Associated with sialolithiasis; may be painful with chewing
- Almost exclusively affects the submandibular gland unilaterally as a hard painless mass simulating malignancy
- Pathogenesis associated with IgG4-related sclerosing diseases; elevated serum IgG4 and IgG4/IgG ratio

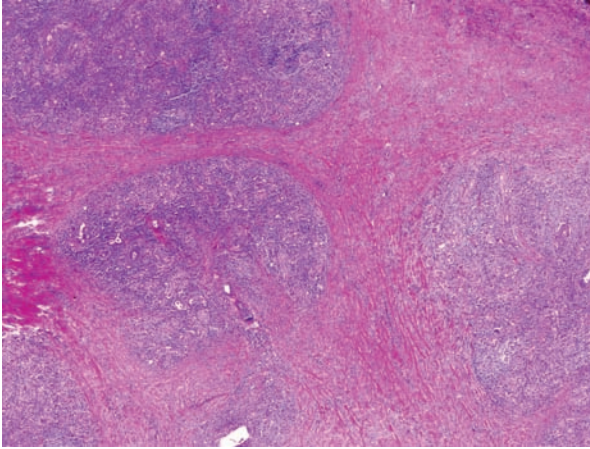
#### GROSS AND HISTOLOGIC FINDINGS:

- Gross: firm nodular expansion of salivary gland
- Retention of normal lobular architecture with variable, but usually heavy lymphoplasmacytic inflammatory infiltrate within the gland (**Figure 4-2**)
- Periductal fibrosis, interlobular sclerosis, atrophy of glandular acini, and reactive lymphoid follicle formation
- Positive IHC: IgG4 plasma cells; T-lymphocytes within ducts and acini, but B-lymphocytes in lymphoid follicles

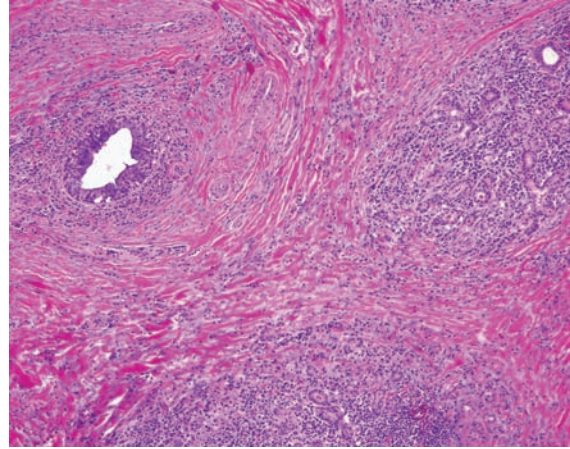
#### DIFFERENTIAL DIAGNOSIS:

- Marginal zone B-cell lymphoma
- Rosai-Dorfman disease

## Chronic Fibrosing Sialadenitis (Kuttner Tumor)



A



B

**FIGURE 4-2** *Kuttner Tumor*

**A.** Thick fibrous bands widely separate glandular lobules. **B.** Acinar parenchymal atrophy and chronic lymphocytic sialadenitis are present along with keloidal-type fibrosis.

### Lymphoepithelial Sialadenitis

#### DEFINITION:

Lymphocytic infiltration of salivary glands associated with an increase in epithelial and myoepithelial cells. Also known as benign lymphoepithelial lesion.

#### CLINICAL FEATURES:

- Most common in the setting of Sjögren syndrome, often as a bilateral firm swelling or mass
- M:F 1:3, decades 4 to 7
- Ninety percent involve the parotid, remainder in submandibular gland
- Thought to be a predecessor of marginal zone B-cell lymphoma

#### GROSS AND HISTOLOGIC FINDINGS:

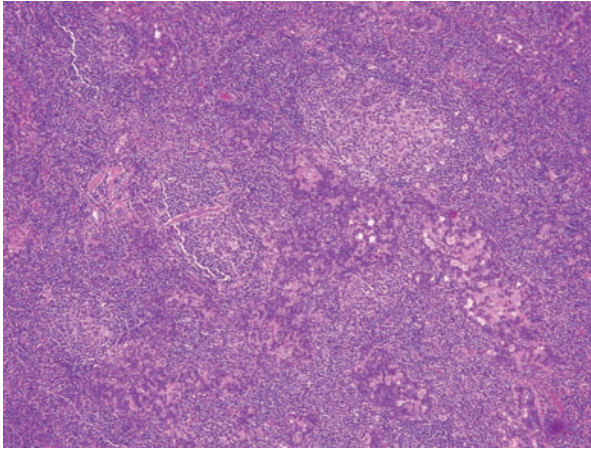
- Gross: nonspecific firm dull pink tissue; retention of lobular cut surface
- Replacement of salivary gland acini by a dense lymphocytic infiltrate associated with irregularly contoured hyperplastic islands of ductular epithelial cells permeated by B-lymphocytes while surrounding lymphocytes are primarily T-cells; epithelial cells are cytologically bland polygonal or spindle-shaped structures (**Figure 4-3**)
- Hyalinization of lymphoepithelial islands sometimes present
- Positive IHC: polyclonal B- and T-cell infiltrate using CD20, CD3 and by flow cytometry; controversial as to whether B-cell clonality is diagnostic of lymphoma

#### DIFFERENTIAL DIAGNOSIS:

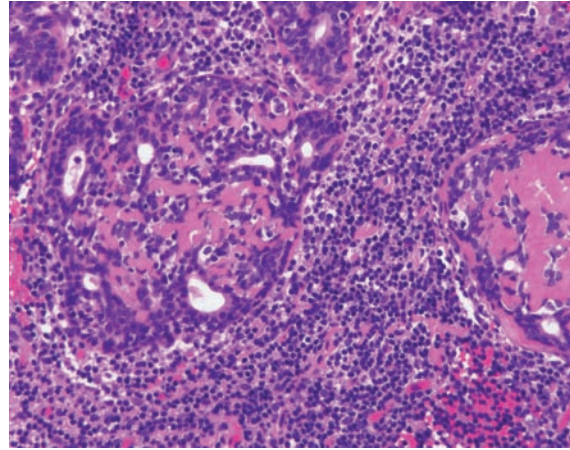
- Marginal zone B-cell lymphoma



## Lymphoepithelial Sialadenitis



A



B

**FIGURE 4-3** *Lymphoepithelial Sialadenitis*

**A.** Abundant lymphoid tissue with follicle formation has replaced normal parotid acini. Epithelial islands blend discreetly with lymphocytes at this magnification.

**B.** Lymphoepithelial islands show partial hyalinization and penetration of lymphocytes into epithelial clusters.

### Pleomorphic Adenoma

#### DEFINITION:

Benign epithelial and myoepithelial salivary gland neoplasm with mesenchymal differentiation, and characterized by histoarchitectural diversity.

#### CLINICAL FEATURES:

- Most common (approximately 50% to 70%) of all salivary gland tumors
- Wide age spectrum (including children) that peaks in decades 4 to 7; more apt to occur in women
- Most common in parotid gland, but may arise in any salivary gland
- Typical clinical history: unilateral single slow-growing painless mass; firm to palpation

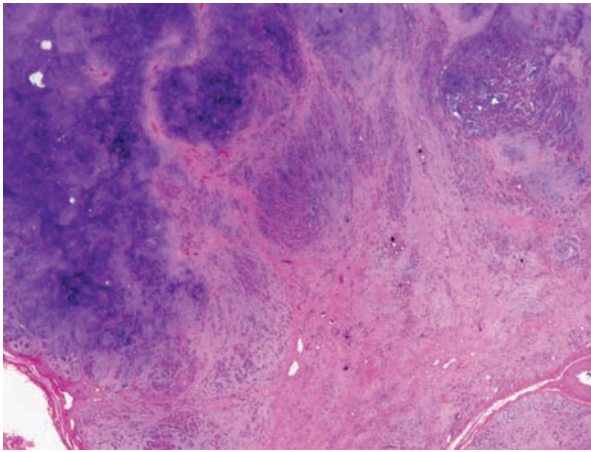
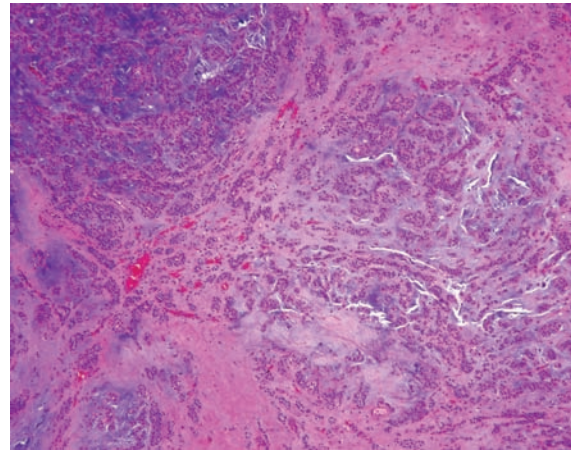
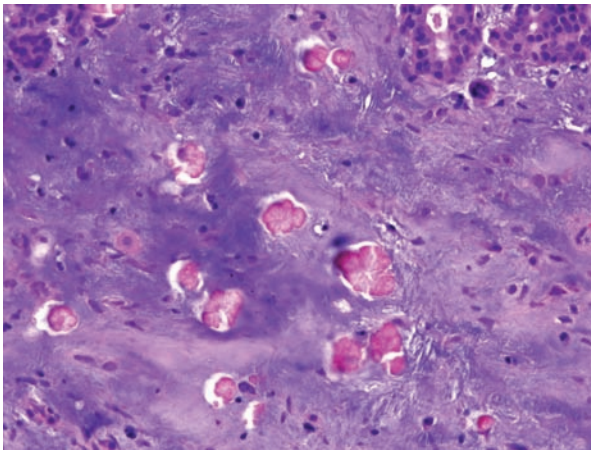
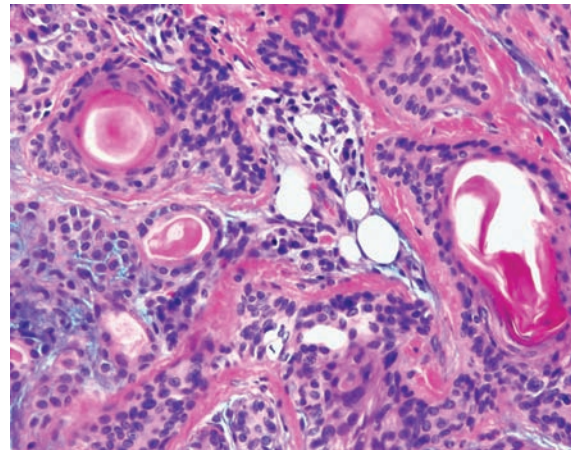
#### GROSS AND HISTOLOGIC FINDINGS:

- Gross: firm, rubbery nodule usually <3 cm with circumscribed borders, thinly encapsulated, blue-white translucent chondroid cut surface; tendency to shell out from surrounding gland
- Mixture of epithelial and myoepithelial cells set in a myxoid/chondromyxoid stroma of variable quantity and sharply separated by a capsule of varying width from the surrounding nonneoplastic gland; occasionally no capsule is present
- Polymorphous architectural spectrum; cells lacking anaplasia are arranged as simple glands, trabeculae of variable thickness, solid cell sheets, cribriform pattern, and cystic change
- Ductules contain a luminal epithelial cell layer and an abluminal myoepithelial cell layer; myoepithelial cells show great “plasticity” with polygonal, columnar, stellate, spindle, plasmacytoid, clear, or basaloid shape and appearance (**Figure 4-4**)
- Ground substance can be focally hyalinized, myxoid, chondromyxoid, or chondroid; may contain stromal tyrosine-like crystalloids
- Metaplasia includes: squamous, mucinous, sebaceous, and oncocytic
- May occur in concert with other salivary gland tumors, so-called hybrid neoplasms
- Necrosis/infarction possible with prior biopsy or manipulation
- Cellular variant: an excess of epithelial/myoepithelial cells with only small foci of stroma
- Positive IHC: abluminal cells: pan-keratin, SMA, actin, p63, calponin, vimentin, and S100; luminal cells: EMA, CD117, pan-keratin, maspin

#### DIFFERENTIAL DIAGNOSIS:

- Adenoid cystic carcinoma
- Polymorphous low-grade adenocarcinoma
- Basal cell adenoma

## Pleomorphic Adenoma

**A****B****C****D**

**FIGURE 4-4** *Pleomorphic Adenoma*

**A.** An overwhelming amount of chondroid and chondromyxoid stroma is present along with stromal fibrosis. Cells are difficult to appreciate at this low magnification. The fibrous capsule is at *lower left*. **B.** Cells and stroma are present in more of a 50-50 mixture; note the variety in cell pattern. **C.** Stromal-based acidophilic fleurette-type crystalloids. **D.** A couple of ducts show keratinizing squamous metaplasia. There is no cytologic atypia.

### Warthin Tumor

#### DEFINITION:

Benign neoplasm characterized by a bilayered oncocytic epithelium with papillary infolding and surrounding lymphoid tissue.

#### CLINICAL FEATURES:

- Men affected slightly more than women; decades 4 to 8
- Common salivary gland tumor
- Almost exclusive to parotid gland; 5% are bilateral; may be fluctuant
- Linked to cigarette smoking

#### GROSS AND HISTOLOGIC FINDINGS:

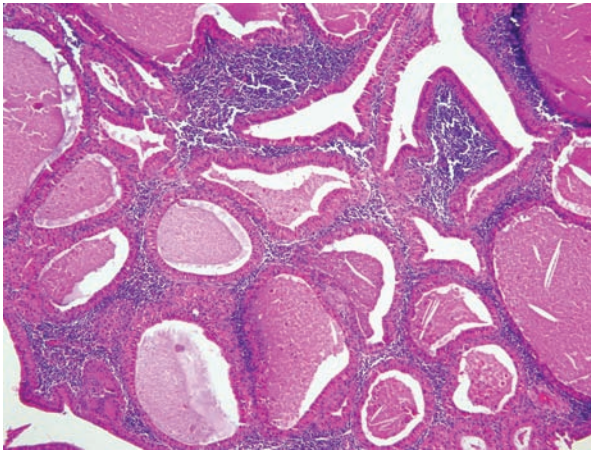
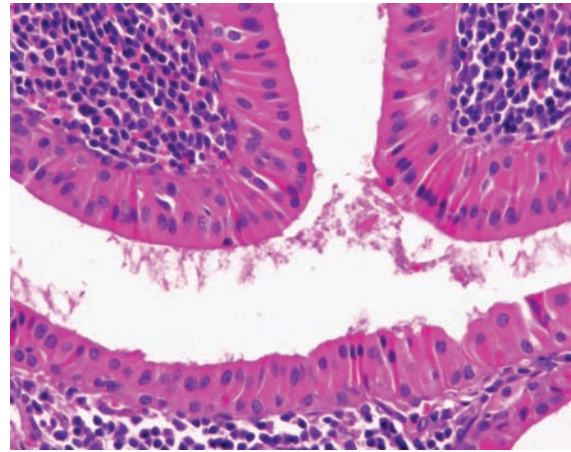
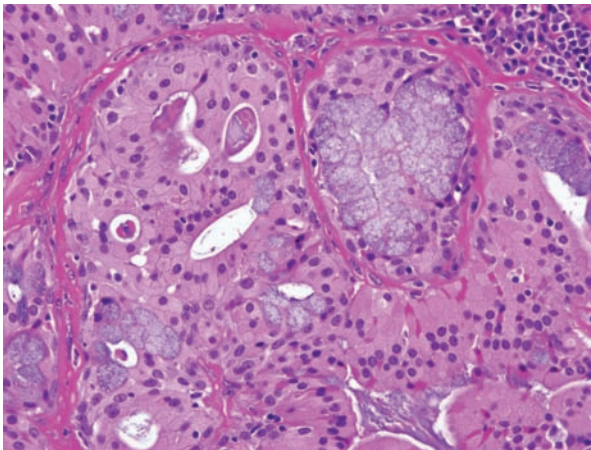
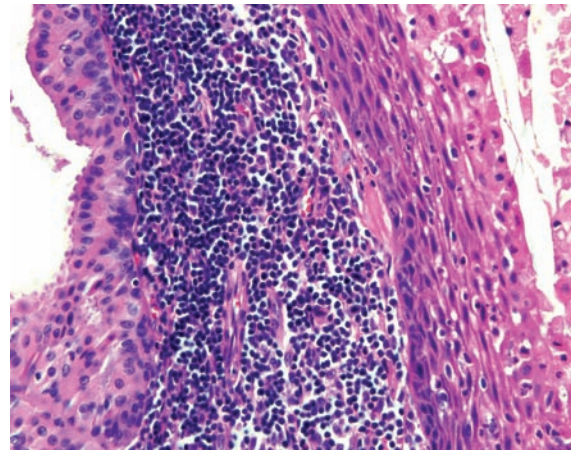
- Gross: well circumscribed with smooth borders; multicystic; cysts filled with mucoid or brownish fluid resembling machine oil
- Bilaminated oncocytic epithelium has a continuous luminal and discontinuous abluminal layer with papillary infolding, variable-sized cystic dilatation, and variable but usually abundant polyclonal lymphoid stroma containing secondary lymphoid follicles (**Figure 4-5**)
- Oncocytes have abundant deeply eosinophilic cytoplasm, rounded uniformly sized nuclei, small but discrete nucleoli, and rarely atypical
- Cystic spaces may be empty, but typically contain amorphous cellular debris, cholesterol crystals, foamy histiocytes, or calcifications
- Squamous, mucinous epithelial metaplasia possible; partial or complete infarction infrequent
- Positive IHC: pan-keratin staining of epithelium; polyclonal lymphoid tissue

#### DIFFERENTIAL DIAGNOSIS:

- Oncocytic cystadenoma
- Oncocytic acinic cell carcinoma



## Warthin Tumor

**A****B****C****D**

**FIGURE 4-5** *Warthin Tumor*

**A.** Oncocytes line dilated glands, some showing papillary infolding, and many filled with granular debris. **B.** Continuous luminal and discontinuous abluminal layer of oncocytes with acidophilic finely granular cytoplasm is surrounded by lymphoid tissue. **C.** Goblet cell metaplasia is present in this oncocyte cluster. **D.** Swath of lymphocytes separates normal oncocytic epithelium (*left*) from epithelium showing squamous metaplasia.



### Basal Cell Adenoma

#### DEFINITION:

Benign neoplasm characterized by an isomorphic population of basaloid cells.

#### CLINICAL FEATURES:

- Uncommon; <5% of salivary gland neoplasms
- Decades 5 to 8; slight female predominance
- Infrequent outside parotid gland

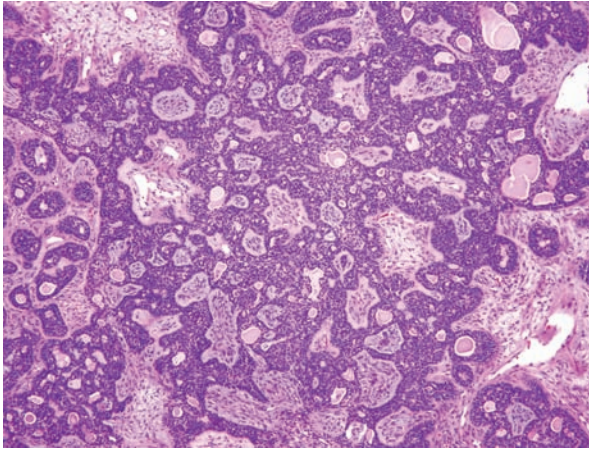
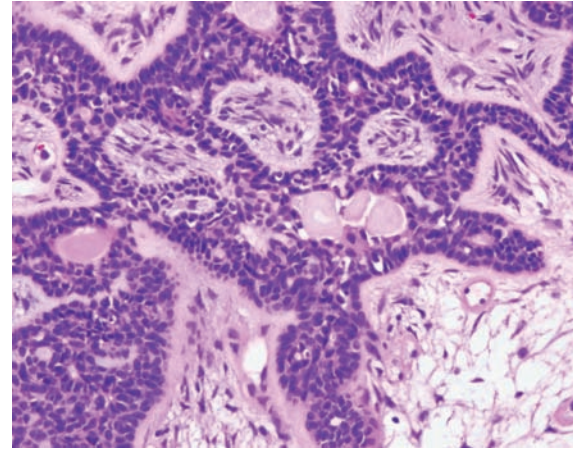
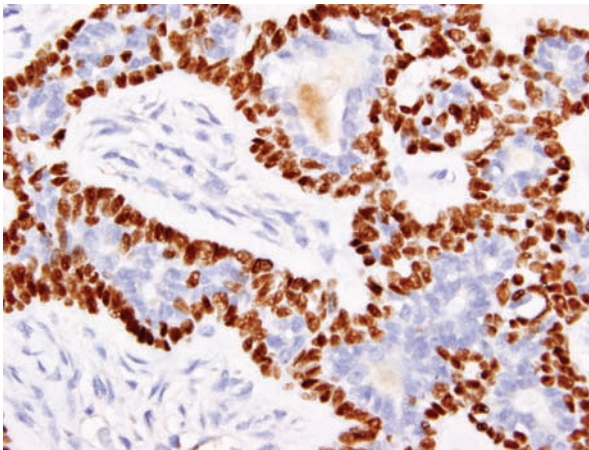
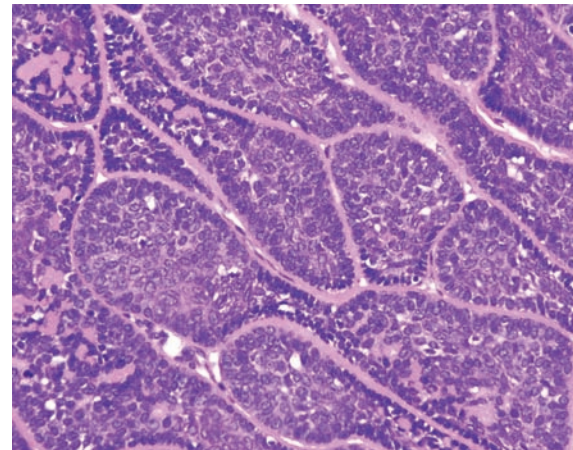
#### GROSS AND HISTOLOGIC FINDINGS:

- Gross: well-circumscribed, firm tan brown to pink
- Encapsulated; various architectural patterns including solid, tubular, membranous, and trabecular; membranous variant most likely to locally recur and characterized by a dense hyaline-like basal lamina girdling cell clusters
- Basaloid cells are uniformly small with round-oval nuclei and minimal visible cytoplasm; palisading occurs at periphery of nests, tubules, and interconnecting trabeculae; absence of chondromyxoid stroma, but collagenous stroma possible (**Figure 4-6**)
- Positive IHC: abluminal cells: SMA, actin, p63, and S100; luminal cells: CD117, CAM 5.2, maspin

#### DIFFERENTIAL DIAGNOSIS:

- Basal cell adenocarcinoma
- Adenoid cystic carcinoma
- Cellular pleomorphic adenoma

## Basal Cell Adenoma

**A****B****C****D**

**FIGURE 4-6** *Basal Cell Adenoma*

**A.** Basaloid cells arranged in trabecular and tubular patterns in a loose fibrous stroma. **B.** Peripheral palisading is obvious. **C.** Nuclear p63 stain highlights the outer myoepithelial layer from image B which is not readily obvious using an H&E stain. **D.** Membranous variant showing a solid pattern and surrounded by thick basal lamina.

### Oncocytoma

#### DEFINITION:

Benign salivary gland neoplasm containing a relatively pure population of oncocytes (a cell swollen with numerous cytoplasmic atypical mitochondria) with no other cellular elements.

#### CLINICAL FEATURES:

- Uncommon; >55 to 60 years of age
- Eighty percent arise in the parotid; painless mass

#### GROSS AND HISTOLOGIC FINDINGS:

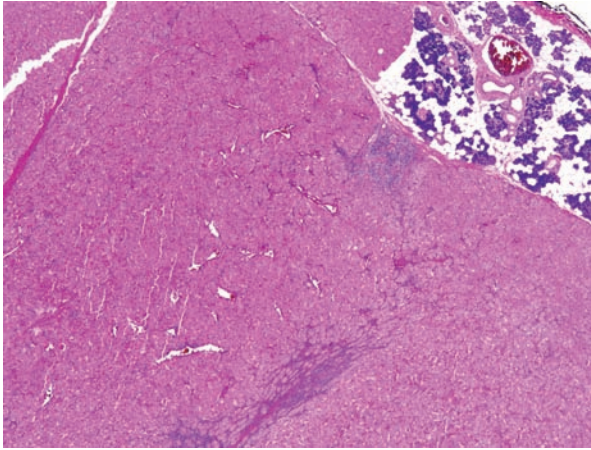
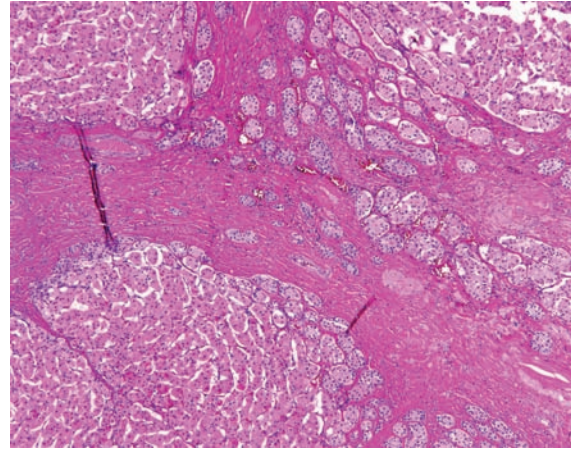
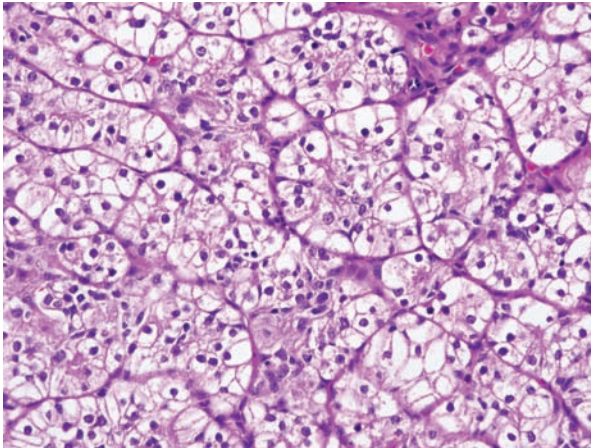
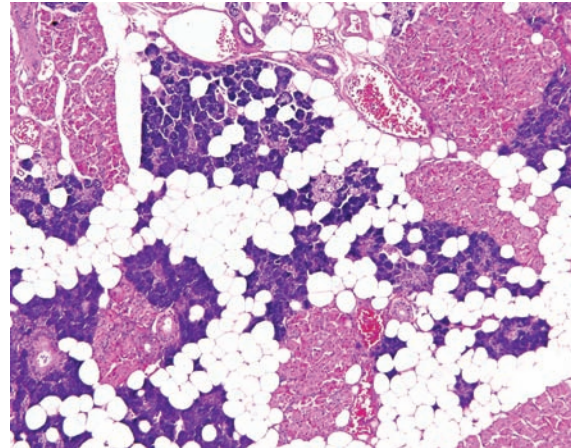
- Gross: circumscribed nodule, tan-yellow to mahogany solid flat cut surface; variable presence of fibrous capsule; sharply delimited from surrounding gland
- Pure population of uniform oncocytes often in a delicate nested pattern; may have a central scar; oncocytes have abundant finely granular, densely eosinophilic/acidophilic cytoplasm, large rounded smoothly contoured nuclei, and slightly enlarged single nucleoli (**Figure 4-7**)
- Absence of lymphocytes within the mass, rare mitoses, no necrosis
- Foci of nodular oncocytosis often present in other areas of the gland
- Clear cell variant: rare cases display predominantly optically clear cytoplasm
- Positive IHC: pan-cytokeratin, EMA; negative with S-100, HMB-45, synaptophysin, mucin

#### DIFFERENTIAL DIAGNOSIS:

- Warthin tumor
- Oncocytic mucoepidermoid carcinoma
- Oncocytosis



## Oncocytoma

**A****B****C****D**

**FIGURE 4-7** *Oncocytoma*

**A.** Tumor edge is sharply defined with a thin capsule. **B.** Tumor center shows a stellate pattern of scarring analogous to similar tumors in the kidney. **C.** Clear cell variant. Organoid pattern is well developed. Unlike metastatic renal cell carcinoma, no vascular congestion or red cell extravasation is present. **D.** Nodular oncocytic hyperplasia. Small unencapsulated oncocytic nodules are present without forming a discrete mass.

### Myoepithelioma

#### DEFINITION:

Benign salivary gland neoplasm having varied morphology but expressing epithelial and myogenic differentiation without a mesenchymal component.

#### CLINICAL FEATURES:

- Uncommon; no gender preference
- Arise primarily in parotid and minor salivary glands of palate
- Broad age range from late childhood to elderly

#### GROSS AND HISTOLOGIC FINDINGS:

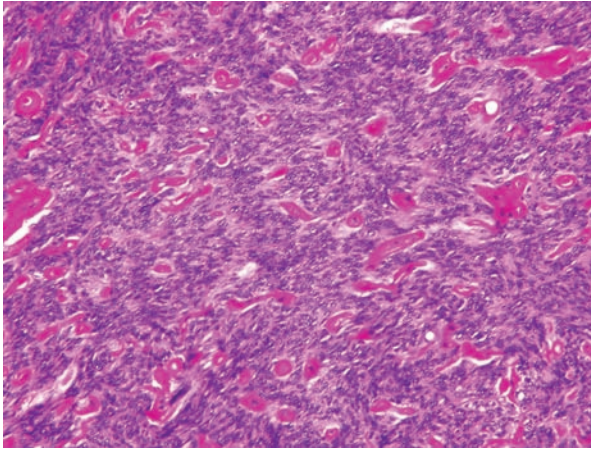
- Gross: circumscribed, tan-yellow nodule; fibrous capsule of variable thickness
- Myoepithelial cells are distinguished by marked variation with angulated, basaloid, epithelioid, spindle, plasmacytoid (hyaline), and clear cell types in solid, nested, and reticular patterns; banal cell nuclei lacking macronucleoli and variable amount of cytoplasm
- There is a lack of chondromyxoid stroma, minimal ductal differentiation or myxoid change (**Figure 4-8**)
- Positive IHC: variable staining with cytokeratin, actin, p63, h-caldesmon, calponin, smooth muscle myosin heavy chain, and maspin

#### DIFFERENTIAL DIAGNOSIS:

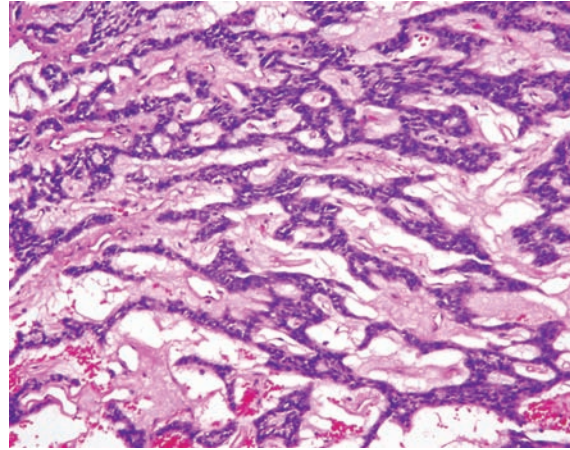
- Spindled soft tissue tumors
- Cellular pleomorphic adenoma



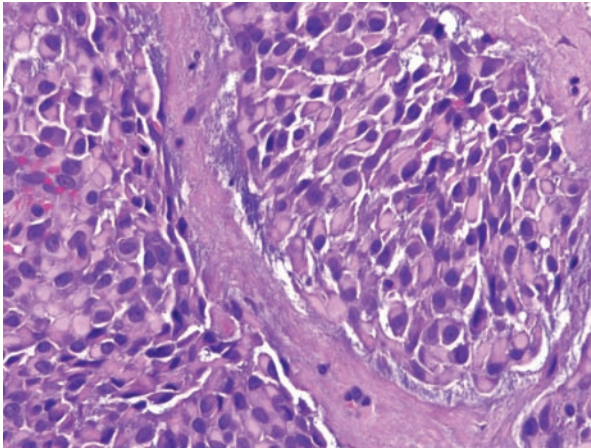
## Myoepithelioma



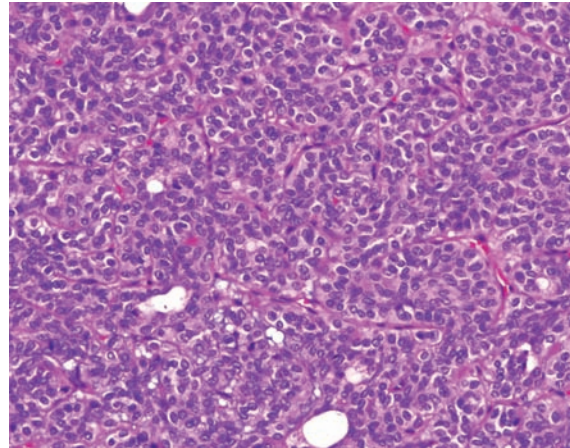
A



B



C



D

**FIGURE 4-8** *Myoepithelioma*

**A.** Spindle cell pattern shows a monotonous population of spindle cells and hyalinized capillaries. **B.** Reticular pattern with stromal hyalinization. **C.** Plasmacytoid or hyaline pattern is characterized by cells with eccentrically placed nuclei and hyaline cytoplasmic globules. **D.** Solid pattern shows uniform rounded and polygonal cells in a nested pattern.

### Mucoepidermoid Carcinoma

#### DEFINITION:

Malignant epithelial salivary gland neoplasm demonstrating both squamous, intermediate cell, and mucinous differentiation.

#### CLINICAL FEATURES:

- Most common salivary gland malignancy, both children and adults
- Arises in parotid but also in submandibular and minor salivary glands throughout the upper aerodigestive tract
- Typically painless mass, usually <3 cm
- Broad age range; peaks at decades 3 to 7 with female predominance

#### GROSS AND HISTOLOGIC FINDINGS:

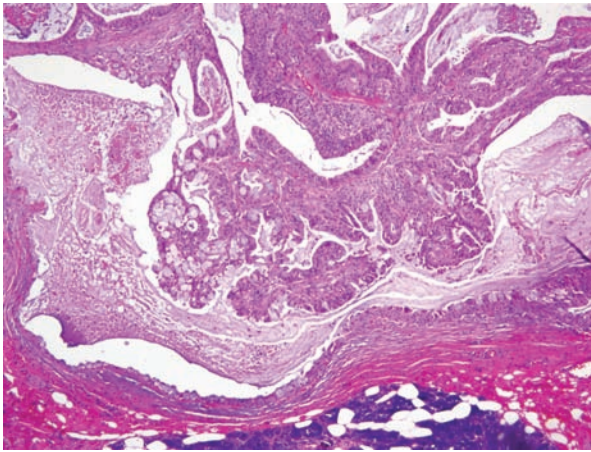
- Gross: only low-grade tumor shows a noninfiltrative border; variable number and size of cysts
- Low-grade neoplasm: solid nests and variable-sized cysts lined by mucin-secreting goblet cells, and intermediate cells (cytologically bland cells larger than a basal cell and smaller than a squamous/epidermoid cell), few mitoses, and only infrequently squamous/epidermoid cells (**Figure 4-9**)
- Mucin pools, oncocytic metaplasia, clear cell metaplasia possible; keratin pearl formation exceedingly rare
- High-grade neoplasm: few/rare mucin-secreting cells or extracellular mucin, few if any cysts, varying degrees of individual cell atypia, increased mitoses, necrosis, and invasive features
- Different grading schemes proposed; none universally accepted. Evans system: low-grade (>10%) high-grade (<10%) intracystic spaces. Brandwein system: grades I to III based on intracystic component, mitoses, degree of invasion, and others findings. AFIP uses a similar system with points given for necrosis, anaplasia, neural invasion, increased mitoses, and <20% cystic component to separate into low, intermediate, and high grades.
- Positive IHC: pan-cytokeratin, p63, CK7, EMA, mucin; negative with CK20, vimentin, actin

#### DIFFERENTIAL DIAGNOSIS:

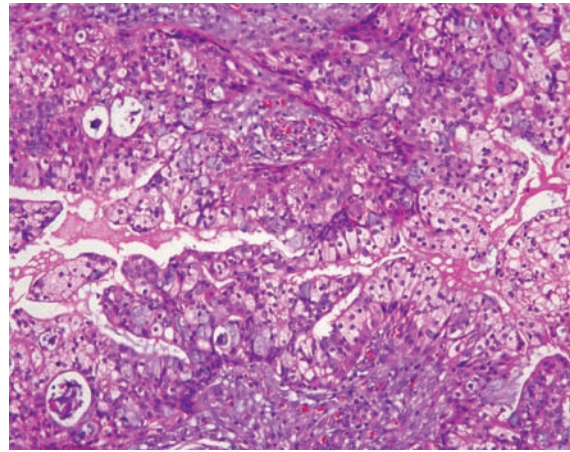
- Low-grade tumor: mucocele, acinic cell carcinoma
- High-grade tumor: squamous carcinoma, salivary duct carcinoma, undifferentiated carcinoma



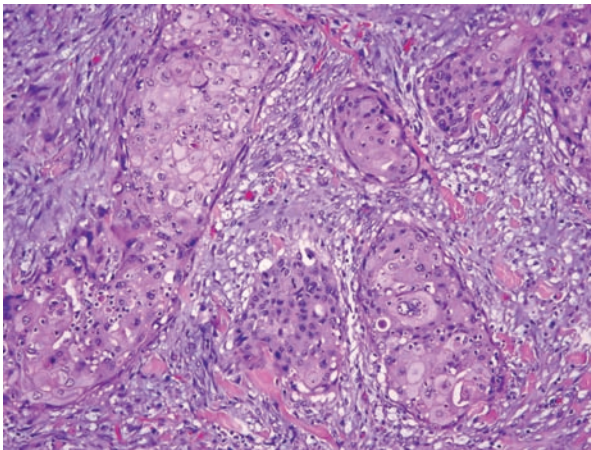
## Mucoepidermoid Carcinoma



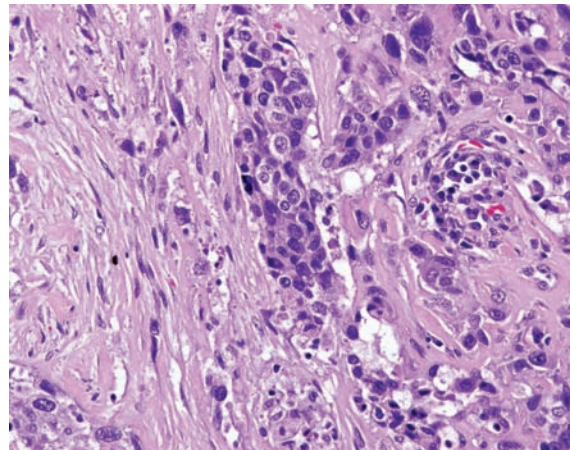
A



B



C



D

**FIGURE 4-9** *Mucoepidermoid Carcinoma*

**A. Low-Grade Carcinoma.** This large mucus-filled cyst shows papillary infolding. **B. Low-Grade Carcinoma.** Intermediate cells and goblet cells are intermixed with one another. Some intermediate cells show clear cell change. **C. High-Grade Carcinoma.** Nests of malignant cells show squamous/epidermoid differentiation. Mucin-containing cells are difficult to find. **D. High-Grade Carcinoma.** Infiltrating malignant cells produce a desmoplastic stroma.

### Acinic Cell Adenocarcinoma (ACC)

#### DEFINITION:

Malignant salivary gland neoplasm showing differentiation toward serous acinar cells; characterized by a polymorphic histologic growth patterns.

#### CLINICAL FEATURES:

- Decades 4 to 7; slight female predominance
- Sites: >80% parotid, minor salivary glands of oral cavity less frequent

#### GROSS AND HISTOLOGIC FINDINGS:

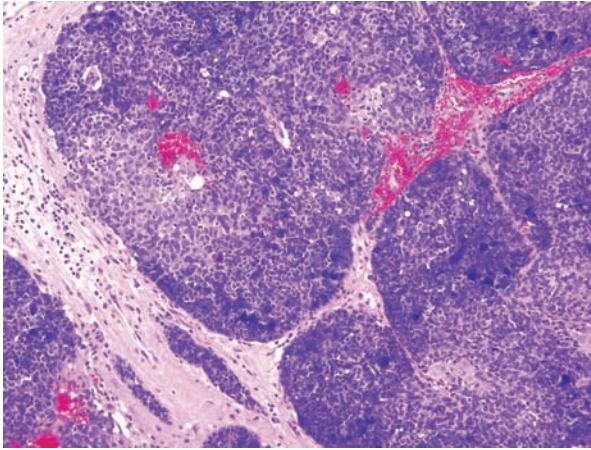
- Gross: well-delineated single or multilobated tan-pink soft or rubbery mass
- Neoplastic cells exhibit serous acinar differentiation at least focally with various patterns including solid, papillary, cystic, cord-like, microcystic, and follicular
- Cytologically banal cells have a low N/C ratio with rounded isomorphic nuclei, small nucleoli, and cytoplasm that can be deeply basophilic with coarse granules, or lightly eosinophilic, coarsely or finely vacuolated, oncocytic, and even clear cell change (**Figure 4-10**)
- Lymphoid tissue with or without lymphoid follicles sometimes abundant
- Dedifferentiated ACC: transformation to undifferentiated carcinoma or poorly differentiated adenocarcinoma
- Positive IHC: pan-cytokeratin, EMA, p63, PAS, PAS-D; negative with mucin, p63, calponin, S-100

#### DIFFERENTIAL DIAGNOSIS:

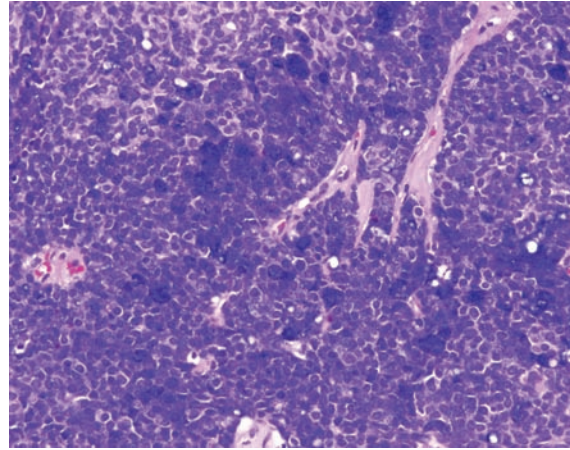
- Low-grade mucoepidermoid carcinoma
- Normal salivary gland
- Adenoid cystic carcinoma



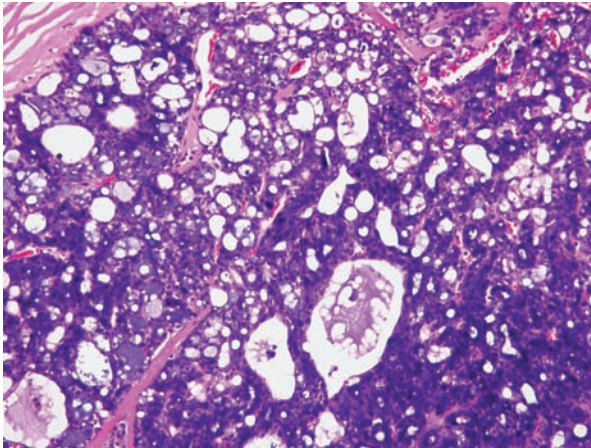
## Acinic Cell Adenocarcinoma (ACC)



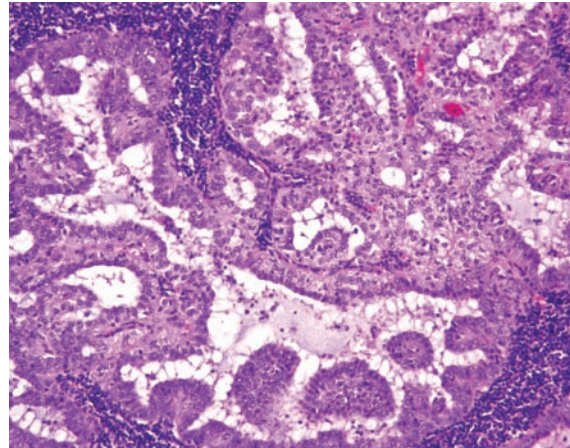
A



B



C



D

**FIGURE 4-10** *Acinic Cell Adenocarcinoma*

**A.** Lobules are solid pattern are intensely basophilic and have a broad invasive front. **B.** High power shows high cellularity, deep cytoplasmic basophilia, and nuclear uniformity. **C.** Microcystic growth pattern. **D.** This papillary growth pattern with lymphoid stroma mimics that of Warthin tumor.



### Adenoid Cystic Carcinoma (AdCC)

#### DEFINITION:

Malignant salivary gland neoplasm composed of both luminal epithelial and abluminal myoepithelial cells with characteristic tubular, cribriform, and solid growth patterns.

#### CLINICAL FEATURES:

- Decades 4 to 6; slight female predominance
- Sites: parotid, submandibular glands, and palate; other sites throughout head and neck less common

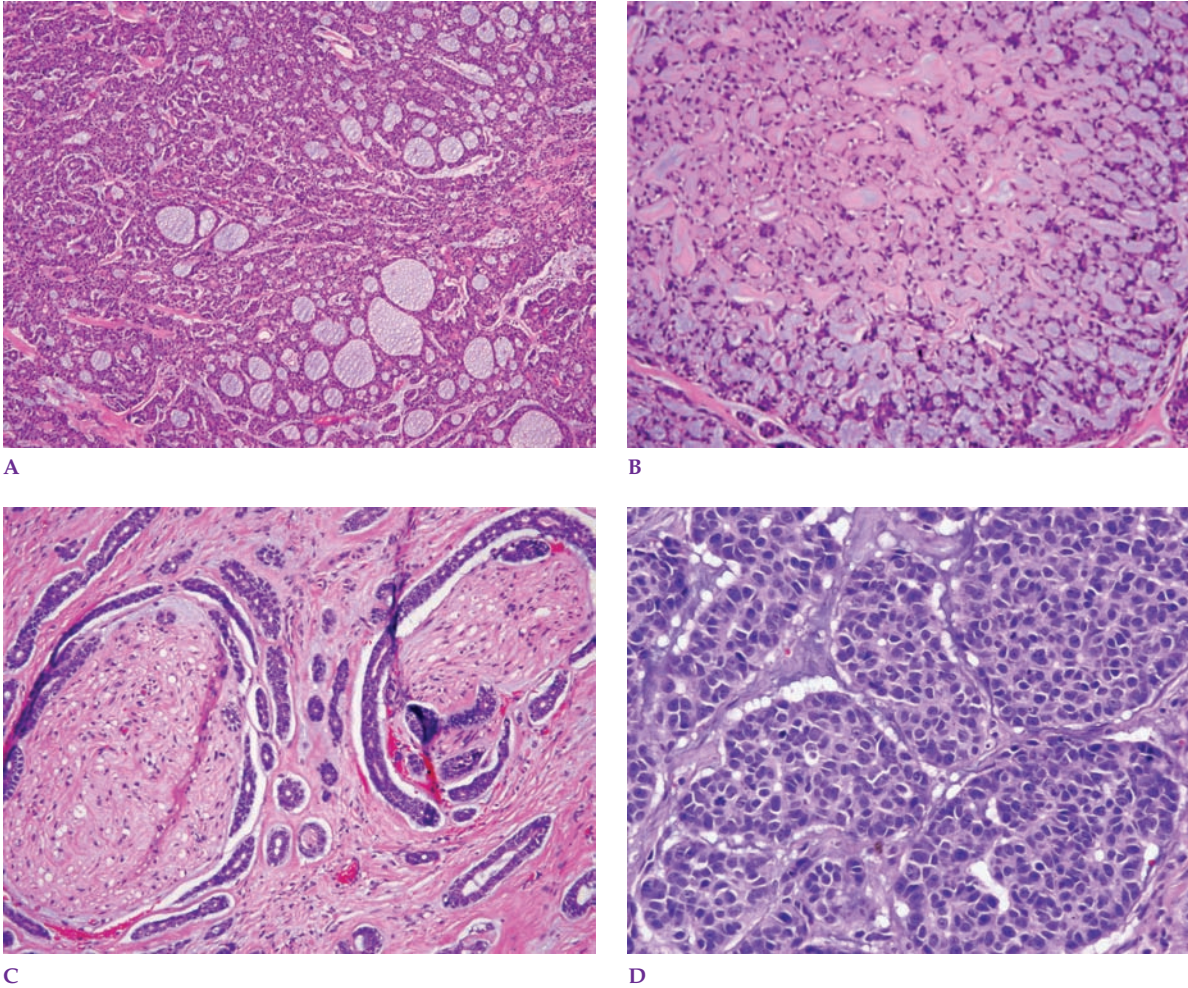
#### GROSS AND HISTOLOGIC FINDINGS:

- Gross: firm, gray-white mass with irregular borders
- Dual layer of monomorphous basaloid cells having hyperchromatic nuclei, indistinct nucleoli, and minimal cytoplasm are arranged in cribriform (basaloid cells containing rigid myxohyaline-filled spaces in a back-to-back sieve-like “Swiss cheese” appearance), tubular, and solid patterns present in various amounts; luminal and abluminal layer with the layer often showing clear cell change; extensive stromal hyalinization possible (**Figure 4-11**)
- Grading based on architectural pattern: grade I: tubular and cribriform, grade II: mainly cribriform with <30% solid, grade III: >30% solid pattern
- Mitoses and necrosis increase with increasing histologic grade
- Perineural invasion nearly always present
- Dedifferentiated AdCC: transformation to undifferentiated carcinoma or poorly differentiated adenocarcinoma
- Positive IHC: abluminal cells: SMA, actin, p63, CD43, calponin, and S100; luminal cells: CD117, EMA, CK7, CAM 5.2, maspin

#### DIFFERENTIAL DIAGNOSIS:

- Polymorphous low-grade adenocarcinoma
- Epithelial-myoepithelial carcinoma
- Pleomorphic adenoma

## Adenoid Cystic Carcinoma (AdCC)



**FIGURE 4-11** *Adenoid Cystic Carcinoma*

**A.** Low-magnification shows classic cribriform and tubular architecture producing so-called “Swiss cheese” appearance. **B.** Copious basal lamina nearly obscures cells.

**C.** Two large nerves show perineural and intraneural invasion. **D.** Dedifferentiated adenoid cystic carcinoma shows a solid pattern with enlarged vesicular nuclei, visible nucleoli, and increased mitoses.

### Polymorphous Low-Grade Adenocarcinoma

#### DEFINITION:

Low-grade cytologically bland adenocarcinoma with a varied, but distinct pattern of infiltrative growth that is extremely rare outside the minor salivary glands.

#### CLINICAL FEATURES:

- Broad age range; peaks in decades 5 to 8
- Females affected about twice as often as men
- Sites: painless mass arising in soft or hard palate followed by buccal mucosa; rare in major salivary glands

#### GROSS AND HISTOLOGIC FINDINGS:

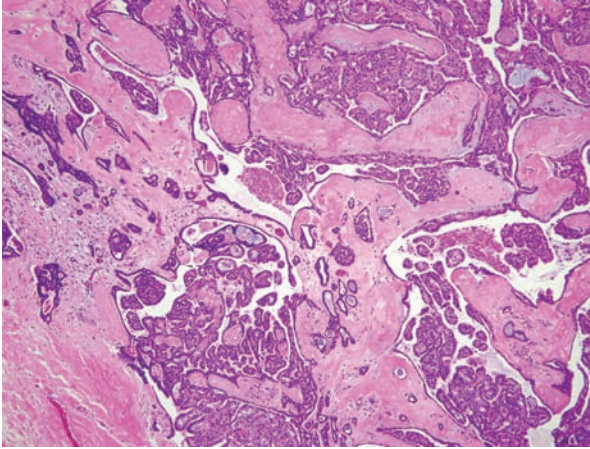
- Gross: circumscribed off-white, tan nodule
- Lacks a fibrous capsule, and shows infiltrative tubular, solid, trabecular, cribriform, and papillary architectural patterns in various proportions; often has a concentrically arranged small tubules and cell cords; lacks a biphasic luminal/abluminal cell population;
- cells have monotonous pale-staining oval to rounded nuclei with fine chromatin stippling (so-called “open” nuclei), thin nuclear membranes, indistinct nucleoli, and minimal eosinophilic cytoplasm; few mitoses and minimal necrosis (**Figure 4-12**)
- Stromal hyalinization commonly produces a “sclerosing adenosis”-like appearance
- Perineural invasion nearly always present
- Positive IHC: pan-cytokeratin, EMA, S-100, p63 (variable); negative with actin, calponin

#### DIFFERENTIAL DIAGNOSIS:

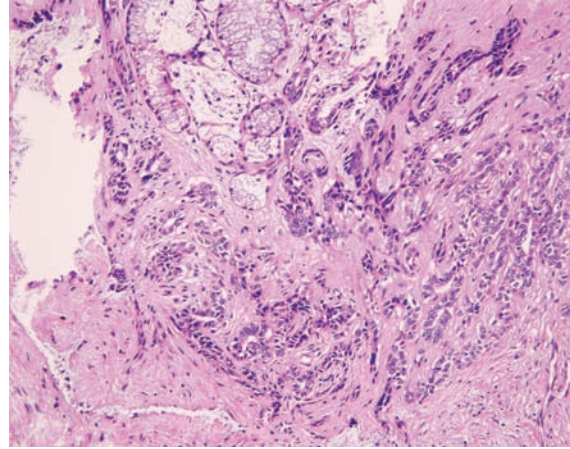
- Pleomorphic adenoma
- Epithelial-myoepithelial carcinoma
- adenoid cystic carcinoma



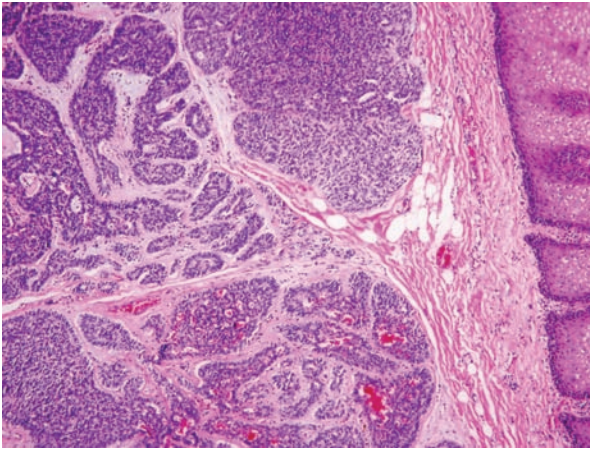
## Polymorphous Low-Grade Adenocarcinoma



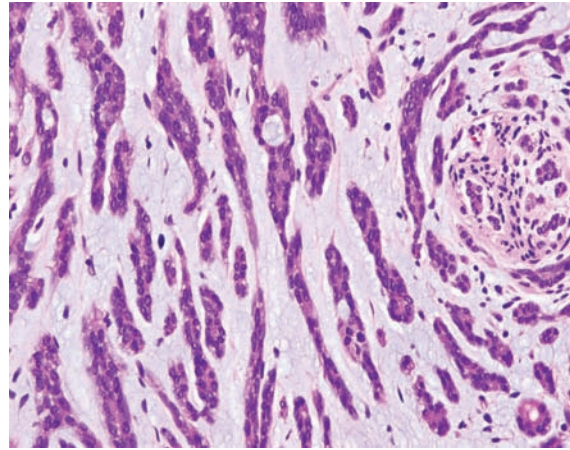
A



B



C



D

**FIGURE 4-12** *Polymorphous Low-Grade Adenocarcinoma*

**A.** This palatal mass shows varied architecture and hyalinized stroma. **B.** Benign mucus glands (*top*) are being infiltrated by microtubular carcinoma. Note the low-grade cytology of individual cells. **C.** This example shows more solid islands of tumor. Normal palatal mucosa is at the *extreme right*. **D.** Cell cords are in a myxoid stroma and show perineural and intraneural invasion (*right*).

### Epithelial-Myoepithelial Carcinoma

#### DEFINITION:

Bicellular malignant salivary gland neoplasm composed of both luminal epithelial and abluminal myoepithelial cells with striking clear cell change of myoepithelial cells.

#### CLINICAL FEATURES:

- <1% of all salivary gland neoplasms; decades 5 to 8
- >70% in parotid, then submandibular gland
- No gender preferences

#### GROSS AND HISTOLOGIC FINDINGS:

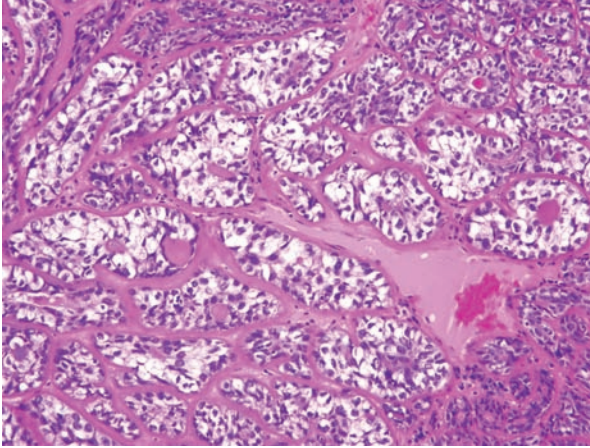
- Gross: circumscribed and sometimes multinodular, firm, off-white cut surface
- Broad infiltrative pattern with multiple nodules, loose myxoid or fibrous stroma, and shows a tubular solid, or trabecular pattern
- Biphasic cell population with a two-layered ductal structure: an inner eosinophilic cuboidal epithelial layer with a high N/C ratio surrounding a lumen and itself surrounded by a clear myoepithelial cell layer that has a prominent basal lamina and obvious optically clear cytoplasm; oncocytic metaplasia rare (**Figure 4-13**)
- Cuboidal luminal cells have isomorphic rounded nuclei; myoepithelial cells larger with coarse chromatin or small nucleoli
- Positive IHC: abluminal cells: SMA, actin, p63, PAS, and S100; luminal cells: CD117, CAM 5.2, EMA, maspin

#### DIFFERENTIAL DIAGNOSIS:

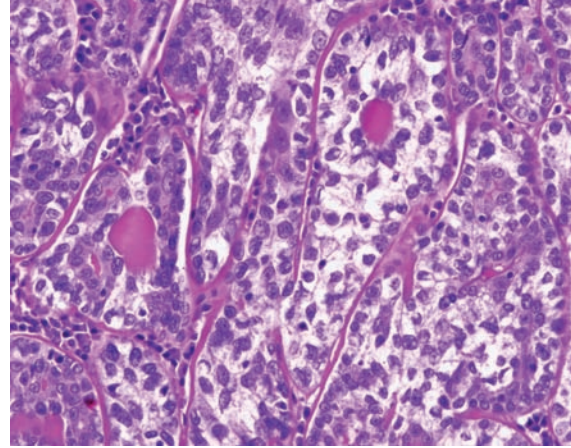
- Clear cell carcinoma, NOS
- Metastatic renal cell carcinoma
- Adenoid cystic carcinoma



## Epithelial-Myoepithelial Carcinoma



A



B

**FIGURE 4-13** *Epithelial-Myoepithelial Carcinoma*

**A.** Cell nests show abundant cytoplasmic clarity. **B.** Larger myoepithelial cells with signature clear cell change have coarse nuclear chromatin; luminal cells difficult to identify.

### Clear Cell Carcinoma, NOS

#### DEFINITION:

Malignant salivary gland neoplasm composed of a repetitive population of cells with optically clear cytoplasm, and lacking myoepithelial cell differentiation. Commonly known as hyalinizing clear cell carcinoma.

#### CLINICAL FEATURES:

- Most common in tongue palate, floor of mouth, less often in parotid, periorbital region
- F:M = 3:1, peak in decade 7 with broad age range

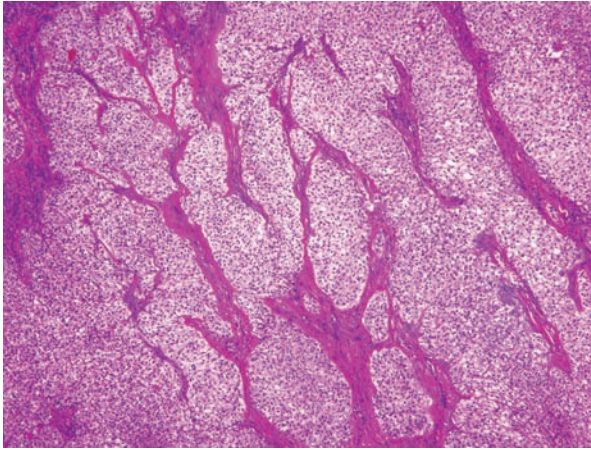
#### GROSS AND HISTOLOGIC FINDINGS:

- Gross: firm to rubbery, tan-gray cut surface, average size 3 cm
- Cords, trabeculae, and nests of monomorphic glycogen-rich clear cells within a stroma that is most often, but not universally abundant sclerosing and hyalinized; cells have minimal atypia and discrete sharp cell border (**Figure 4-14**)
- Mitotic figures, perineural invasion, vascular invasion, and necrosis are uncommon
- Positive IHC: pan-cytokeratin, CAM 5.2, EMA, PAS, CEA (variable); negative with SMA, desmin, mucin, S-100, and PAS-D

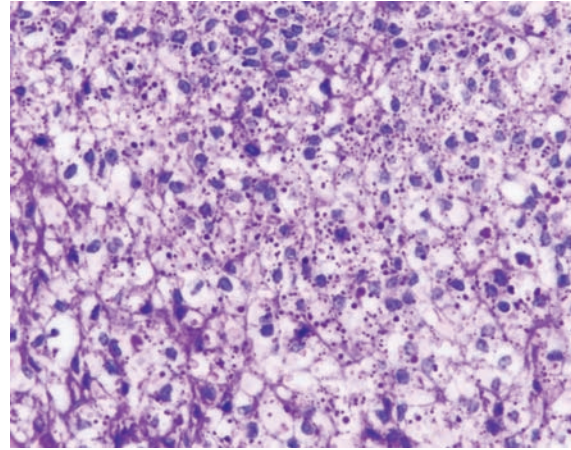
#### DIFFERENTIAL DIAGNOSIS:

- Metastatic renal cell carcinoma
- Epithelial-myoepithelial carcinoma
- Acinic cell adenocarcinoma

## Clear Cell Carcinoma, NOS



A



B

**FIGURE 4-14** *Clear Cell Carcinoma*

**A.** Solid sheets of clear epithelial cells are separated by branching fibrous trabeculae.

**B.** PAS stain is diffusely positive in these glycogen-filled clear cells. Note sharp discrete cell borders.

### Salivary Duct Carcinoma

#### DEFINITION:

High-grade malignant salivary gland neoplasm with histopathologic features mimicking in situ and invasive ductal carcinoma of the breast.

#### CLINICAL FEATURES:

- Decades 6 to 7; M:F = 5:1
- About 80% arise in parotid or submandibular gland
- May present with facial nerve paralysis

#### GROSS AND HISTOLOGIC FINDINGS:

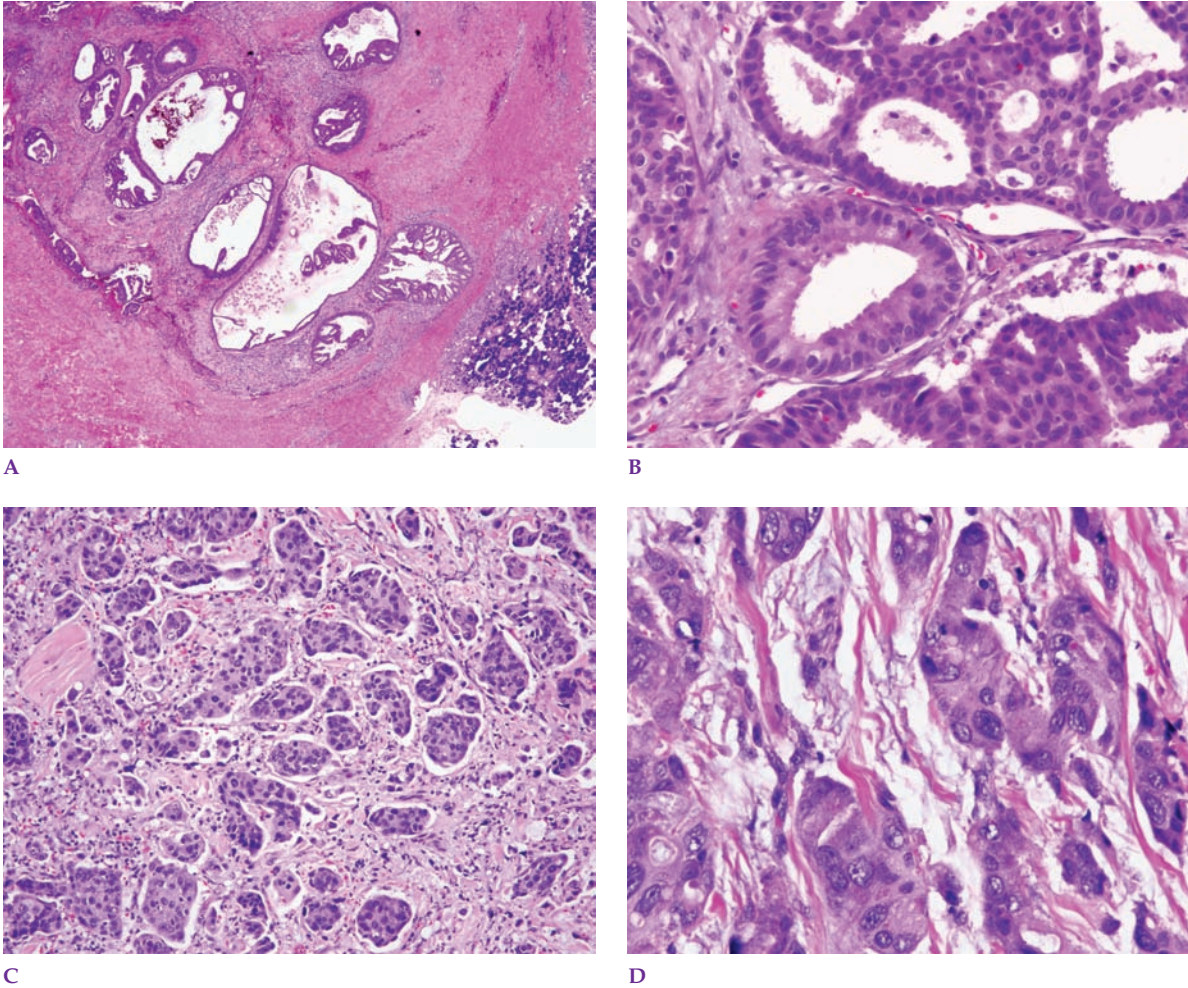
- Gross: ill-defined, firm, yellow-white mass; necrosis may be grossly visible
- Infiltrative growth: solid, papillary, and cribriform pattern with central comedonecrosis strongly mimicking the pattern of mammary ductal carcinoma in situ and invasive carcinoma with a desmoplastic stroma; large cells have abundant eosinophilic cytoplasm, large pleomorphic nuclei, and single macronucleoli (**Figure 4-15**)
- Variants: sarcomatoid (malignant spindle cells, multinucleated tumor giant cells), invasive micropapillary (morule-like cell groups surrounded by a clear space and lacking fibrovascular cores), and mucin-rich (clusters of carcinoma cells embedded in mucin-filled pools)
- Perineural, vascular invasion common
- Positive IHC: pan-keratin, androgen receptor, EMA, CEA, GCDFP-15 positive; negative for ER, PR, myoepithelial markers

#### DIFFERENTIAL DIAGNOSIS:

- Metastatic carcinoma
- Oncocytic carcinoma
- High-grade mucoepidermoid carcinoma



## Salivary Duct Carcinoma



**FIGURE 4-15** *Salivary Duct Carcinoma*

**A.** Markedly dilated large ducts set in a desmoplastic stroma show a cribriform pattern. **B.** Cells have abundant almost oncocytic cytoplasm. **C.** Micropapillary pattern shows cellular balls of carcinoma surrounded by a cleft-like space. **D.** Cellular pleomorphism is readily apparent.

### Carcinoma Ex Pleomorphic Adenoma

#### DEFINITION:

High-grade malignant salivary gland neoplasm arising in a preexisting pleomorphic adenoma.

#### CLINICAL FEATURES:

- Majority are parotid and submandibular neoplasm
- Decades 6 to 8; slight female predominance
- History of long-standing mass or prior surgery for pleomorphic adenoma common
- May present with facial nerve paralysis

#### GROSS AND HISTOLOGIC FINDINGS:

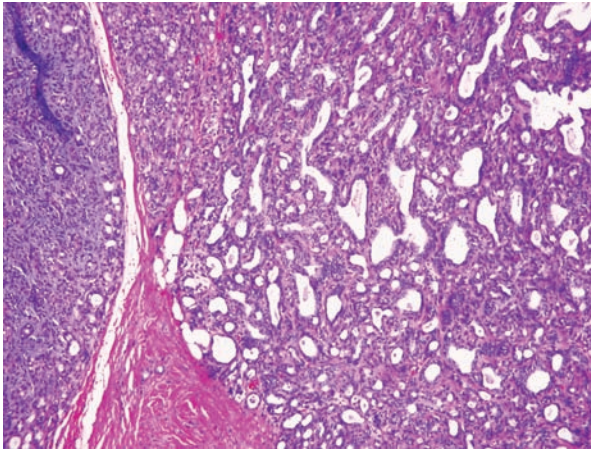
- Gross: poorly circumscribed yellow-tan areas with blue-white chondroid foci of pleomorphic adenoma
- Variable amount of pleomorphic adenoma histology with foci of carcinoma having obvious cellular pleomorphism, necrosis, and numerous mitoses; most common carcinomatous component is adenocarcinoma, NOS, high-grade mucoepidermoid carcinoma, and salivary duct carcinoma (**Figure 4-16**)
- Three variants: (1) in situ: atypical nuclei replace luminal cells but retain an abluminal myoepithelial layer with no penetration beyond capsule; (2) minimally invasive (microinvasive): tumor invasion <1.5 mm beyond capsule; (3) frankly invasive: tumor invasion >1.5 mm beyond capsule
- Positive IHC: carcinomatous component is pan-cytokeratin positive while negative for most myoepithelial markers

#### DIFFERENTIAL DIAGNOSIS:

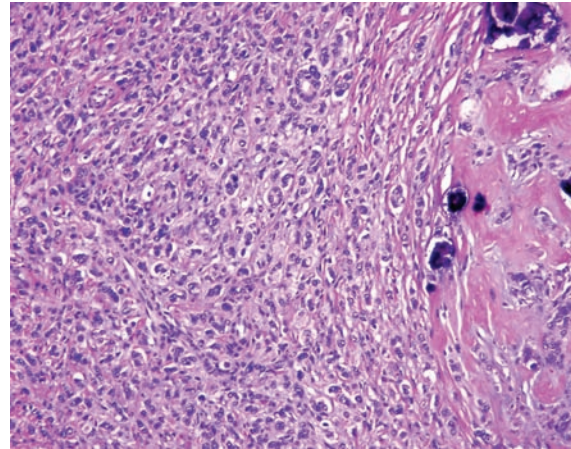
- Pleomorphic adenoma
- Adenocarcinoma, NOS



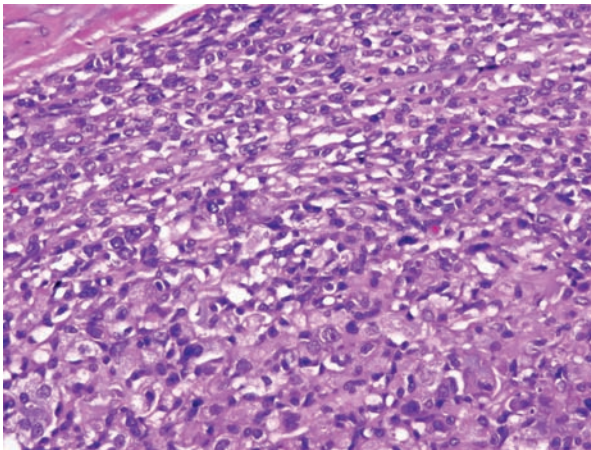
## Carcinoma Ex Pleomorphic Adenoma



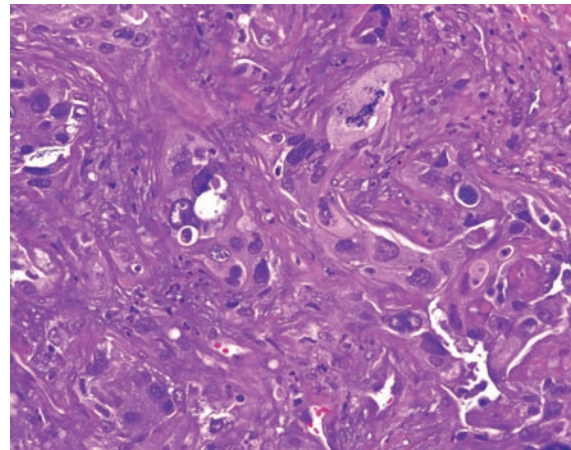
A



B



C



D

**FIGURE 4-16** *Carcinoma Ex Pleomorphic Adenoma*

**A.** Adenocarcinoma (*right*) arises in conjunction with a pleomorphic adenoma (*left*). **B.** Adenocarcinoma, NOS occupies most of this field with stromal hyalinization and calcification (*right*). **C.** Benign myoepithelial cells of residual adenoma (*upper half*) contrast with the large cells of carcinoma (*lower half*). **D.** High-grade mucoepidermoid carcinoma is present in this mass that showed foci of pleomorphic adenoma in other areas.



## Gnathic Bones

### NONNEOPLASTIC LESIONS

FIBROUS DYSPLASIA, CRANIOFACIAL

### BENIGN NEOPLASMS

OSTEOMA/EXOSTOSIS

OSSIFYING FIBROMA (CEMENTO-OSSIFYING FIBROMA)

AMELOBLASTOMA

AMELOBLASTIC FIBROMA

CALCIFYING EPITHELIAL ODONTOGENIC (PINDBORG)  
TUMOR

KERATOCYSTIC ODONTOGENIC TUMOR (ODONTOGENIC  
KERATOCYST)

ODONTOGENIC MYXOMA

ODONTOMA, COMPLEX TYPE

### MALIGNANT NEOPLASMS

CRANIOFACIAL OSTEOSARCOMA, CONVENTIONAL TYPE



### Fibrous Dysplasia, Craniofacial

#### DEFINITION:

A genetic ossification disorder in which disorganized woven bone and fibrous tissue replaces normal medullary bone.

#### CLINICAL FEATURES:

- Monostotic form (75–80% of cases), and polyostotic form (associated with McCune-Albright syndrome)
- Monostotic form: decades 1 to 3 of life; slight female predominance, nasal obstruction
- Painless swelling of the gnathic bones (maxilla > mandible), displacement of teeth, cranial nerve dysfunction
- Plain X-ray critical to diagnosis: unilocular radiodense, “ground-glass” change with indistinct borders

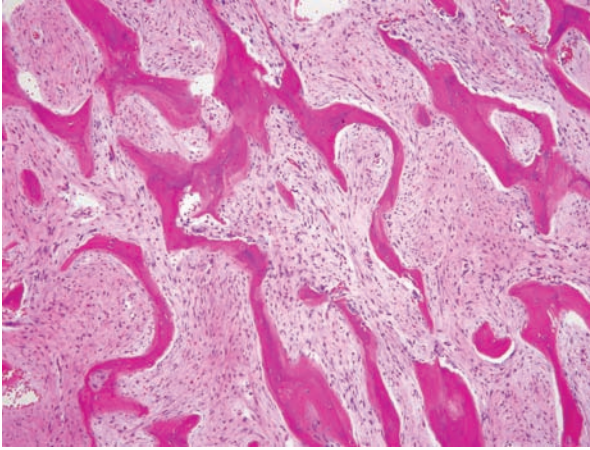
#### GROSS AND HISTOLOGIC FINDINGS:

- Gross: curetted partially softened bony fragments that can be cut with a knife
- Irregular curvilinear or serpiginously contoured spicules of immature (woven) bone randomly arranged in loosely cellular fibrous stroma composed of uniform spindle cells that lack a specific pattern, cellular atypia, and mitoses
- Bone spicules either unlined or sparsely/focally lined by osteoblasts, may be semi-calcified, and more cellular than normal cancellous bone (**Figure 5-1**)
- May show maturation to lamellar bone
- Positive IHC: not applicable for diagnosis

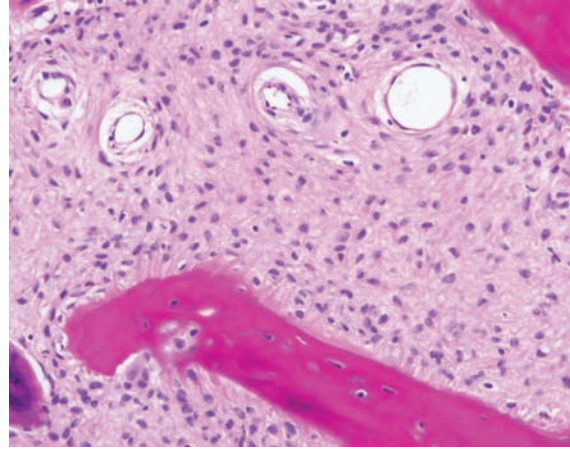
#### DIFFERENTIAL DIAGNOSIS:

- Ossifying fibroma
- Osseous dysplasia
- Low-grade osteosarcoma

## Fibrous Dysplasia, Craniofacial



A



B

**FIGURE 5-1** *Fibrous Dysplasia*

**A.** Irregularly contoured bone spicules; many have a “hooked” shape embedded in a moderately cellular fibrous matrix. **B.** Spindle and stellate stromal cells show uniformity in size and appearance. Note the absence of osteoblastic rimming of bone.

### Osteoma/Exostosis

#### DEFINITION:

A benign lesion composed of mature compact or cancellous bone. Some authorities consider these as hamartomas or examples of bony dysplasia, while others feel they represent neoplasms. A lesion affecting bones formed by membranous ossification (mandible, calvaria) is typically termed an exostosis.

#### CLINICAL FEATURES:

- M:F = 2:1; decades 2 to 4 of life
- May be intraosseous or attached to bone surface; usually asymptomatic
- Affects orbit, paranasal sinuses, facial bones; multiple lesions affecting mandible and calvaria associated with Gardner syndrome
- Plain X-ray: radiodense, sharply defined borders

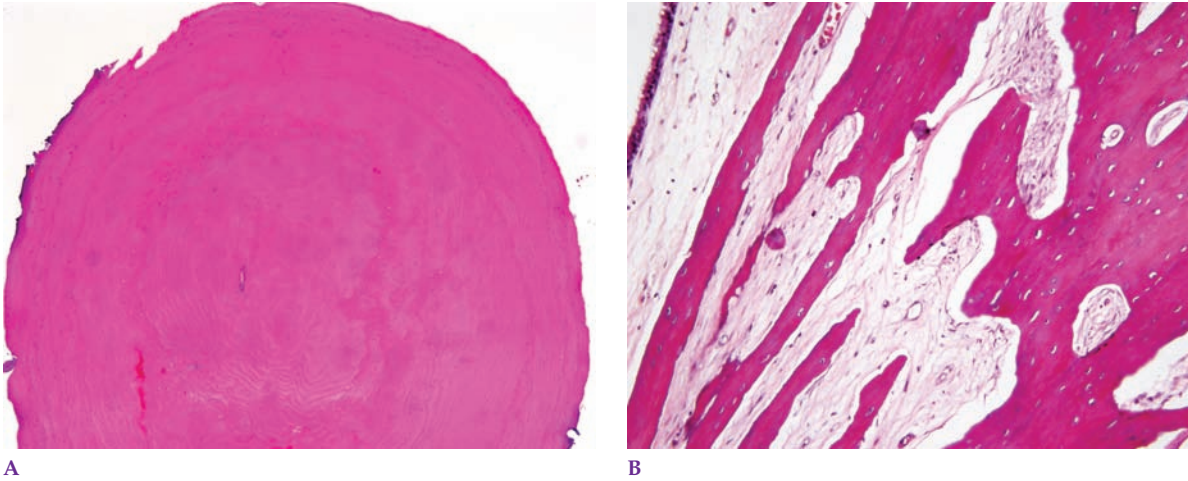
#### GROSS AND HISTOLOGIC FINDINGS:

- Gross: exostosis is a sessile, button-like bony excrescence
- Circumscribed nodular mass of sclerotic lamellar bone spicules and cortical bone with osteons (central Haversian canals, and circumferentially arranged lamellar bone containing osteocytes within lacunae) (**Figure 5-2**)
- Minimal amount of intraosseous space (when present) contains fibrovascular tissue
- Positive IHC: not applicable for diagnosis

#### DIFFERENTIAL DIAGNOSIS:

- Palatal and mandibular torus

## Osteoma/Exostosis



**FIGURE 5-2** *Osteoma/Exostosis*

**A.** Exostosis from the mandible shows an annular spherule of dense, sclerotic bone.

**B.** Lamellar bone from an osteoma of the paranasal sinus has a small amount of interosseous connective tissue. Sinus mucosa is at the extreme *top left*.



### Ossifying Fibroma (Cemento-Ossifying Fibroma)

#### DEFINITION:

A benign fibro-osseous neoplasm composed of mineralized woven bone, lamellar bone, cementum-like bodies, and cellular fibrous tissue. Three clinicopathologic types include conventional type, juvenile trabecular type, and juvenile psammomatoid type.

#### CLINICAL FEATURES:

- Decades 2 to 4 of life; F:M = 4:1.
- Mandible (70–80% of cases) >> maxilla
- Painless jaw enlargement; may cause displacement of teeth
- Juvenile types: rapidly growing, primarily in children, paranasal sinus bones
- Plain X-ray critical to diagnosis: mixed radiodense-radiolucent, well-defined sclerotic borders

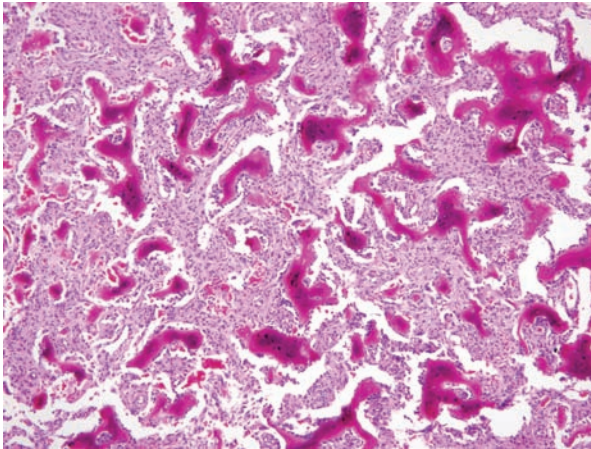
#### GROSS AND HISTOLOGIC FINDINGS:

- Gross: shells out from surrounding bone intact or in large pieces, firm, smooth surfaced
- Thin trabeculae of primarily woven bone are mostly lined by osteoblasts in a cytologically bland fibroblastic stroma that occasionally shows a storiform pattern; stroma has variable cellularity (usually hypercellular)
- Lamellar bone and scattered basophilic spherules of cementum-like material, typical of psammomatoid variant less common (**Figure 5-3**)
- Juvenile type: woven bone trabeculae rimmed by enlarged osteoblasts, highly cellular fibroblastic stroma with mitoses; psammomatous ossicles of bone with variable stroma
- Positive IHC: not applicable for diagnosis

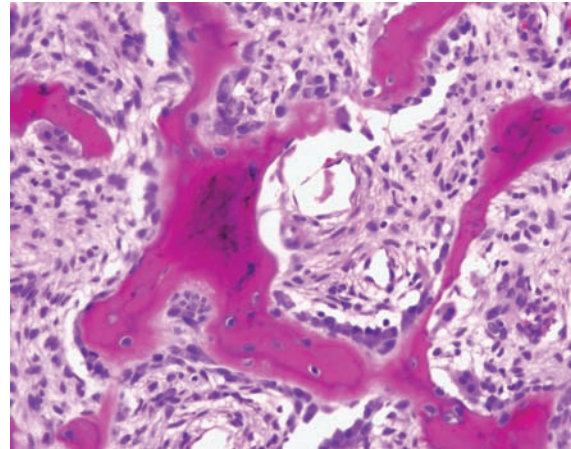
#### DIFFERENTIAL DIAGNOSIS:

- Fibrous dysplasia.
- Cemento-osseous dysplasia

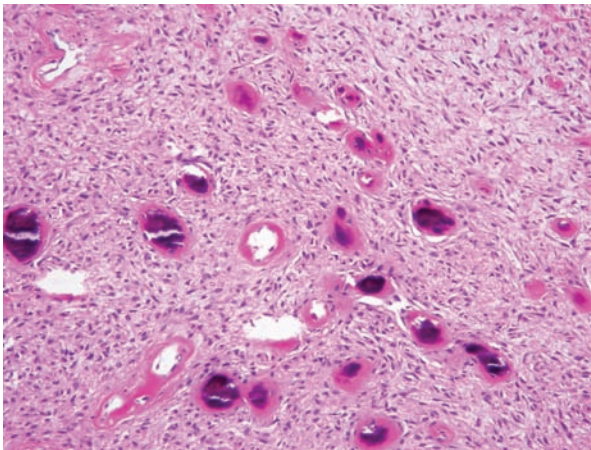
## Ossifying Fibroma (Cemento-Ossifying Fibroma)



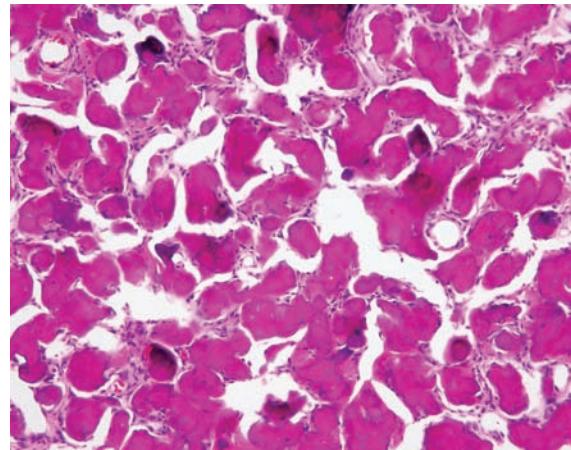
A



B



C



D

**FIGURE 5-3** *Ossifying Fibroma*

**A.** Hypercellular fibrous stroma contains haphazardly arranged bony trabeculae. **B.** Enlarged osteoblasts partially surround spicules of woven bone. **C.** Spherical partly calcified cementum-like particles in abundant stroma. **D.** Psammomatoid variant contains minimal fibrous tissue.

### Ameloblastoma

#### DEFINITION:

A benign, but locally aggressive epithelial odontogenic neoplasm that demonstrates the ameloblast differentiation seen in normal odontogenesis.

#### CLINICAL FEATURES:

- M = F; peak in decades 3 to 4 of life; broad age range
- Most common odontogenic tumor; molar region of mandible (75%) > maxilla
- Painless, slow growing jaw mass; associated with unerupted tooth
- Four clinical subtypes: solid/multicystic (about 80–90% of cases), peripheral (occurs as an extrasosseous neoplasm), desmoplastic, and unicystic
- Plain X-ray: large radiolucent uni- or multilocular (most common) mass; the latter has a classic “soap-bubble” appearance

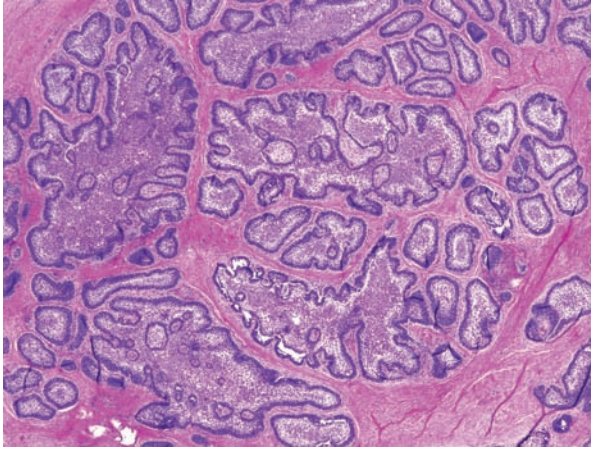
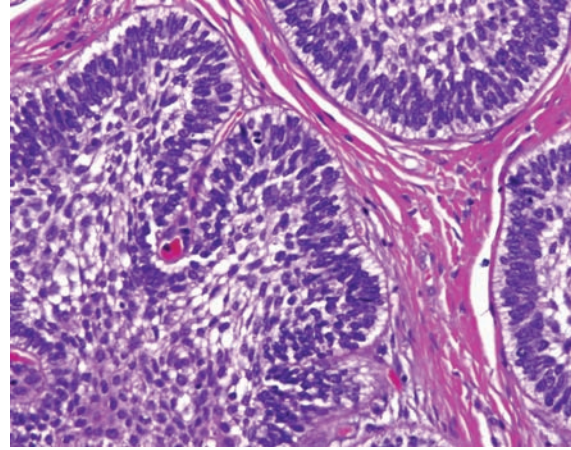
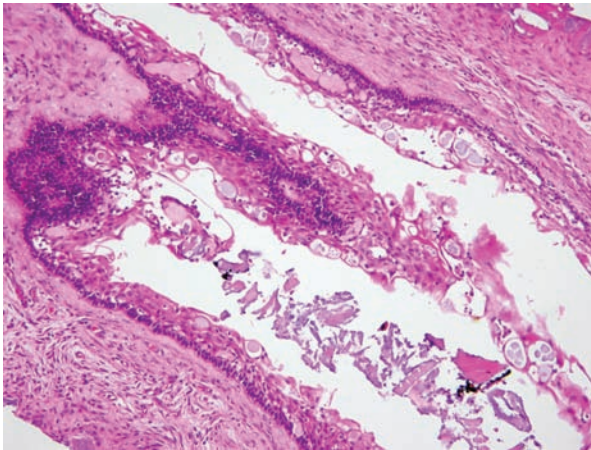
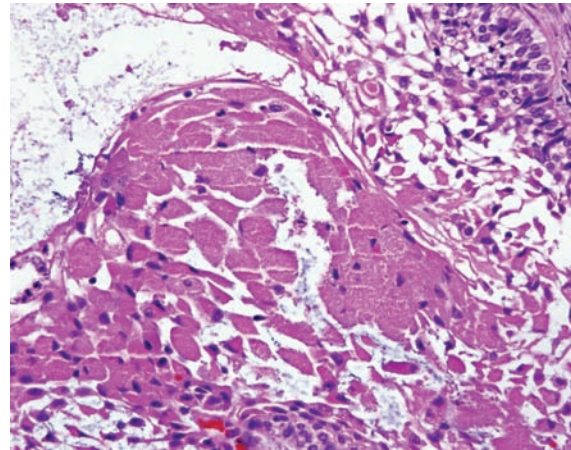
#### GROSS AND HISTOLOGIC FINDINGS:

- Gross: solid intraosseous grey-white mass and/or cystic with yellow-clear serous or brownish gelatinous fluid
- Multiple histopathologic variants with no prognostic significance; most common are follicular and plexiform subtypes
- Follicular type: islands of uniformly bland epithelial cells in a mature fibrous, focally hyalinized stroma surrounded by a rigid perpendicular palisading of hyperchromatic columnar cells; the latter shows “reverse polarization”, that is, nuclei are in the apical half of the cell orientated away from the basement membrane (**Figure 5-4**)
- Squamous islands contain spindle, stellate cells loosely connected to one another by thin cytoplasmic processes resembling stellate reticulum of the developing tooth; often undergo cystic change and may coalesce with one another forming small and large cysts
- Granular cell, squamous (acanthomatous) variants
- Plexiform variant: cords and ribbon-like strands of interconnecting basaloid cells generally lacking stellate reticulum; reverse polarization sometimes difficult to appreciate
- Unicystic ameloblastoma: a cyst lined by ameloblastic epithelium
- Positive IHC: pan-keratin stains, not necessary for diagnosis

#### DIFFERENTIAL DIAGNOSIS:

- Squamous cell carcinoma
- Ameloblastic fibroma
- Ameloblastic carcinoma



**Ameloblastoma****A****B****C****D**

**FIGURE 5-4** *Ameloblastoma*

**A.** Follicular pattern shows solid islands of odontogenic epithelium with conspicuous peripheral basophilia. **B.** Reverse polarization highlighted by subnuclear vacuoles in columnar cells; stellate reticulum at *bottom left*. **C.** Cystic change within epithelial nest and acanthomatous differentiation. **D.** Granular cell variant.

### Ameloblastic Fibroma

#### DEFINITION:

A benign odontogenic neoplasm composed of both mesenchymal tissue resembling ectomesenchyme of the dental papillae and epithelial rests resembling dental lamina, plus lacking enamel, dentin, and cementum.

#### CLINICAL FEATURES:

- M:F = 1.5:1; 60% in decades 1 to 2 of life, broad age range
- Asymptomatic or painless swelling of jaw
- Plain X-ray: radiolucent, uni- or multilocular lesion in posterior mandible displacing teeth

#### GROSS AND HISTOLOGIC FINDINGS:

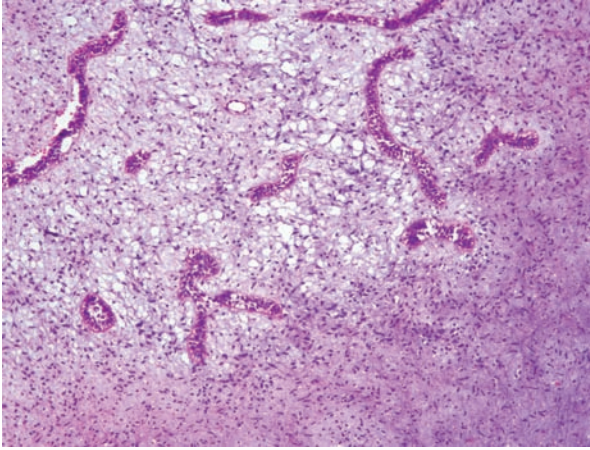
- Gross: soft, grey, sometimes translucent
- Abundant immature appearing, cellular, myxoid/fibromyxoid-rich connective tissue containing branching, interconnecting strands of bland ameloblastic epithelial cells lacking well-developed stellate reticulum
- Stromal cells are spindle and stellate in a primitive ectomesenchyme with minimal vascularity, few mitoses, and no cytologic atypia (**Figure 5-5**)
- Positive IHC: not applicable for diagnosis

#### DIFFERENTIAL DIAGNOSIS:

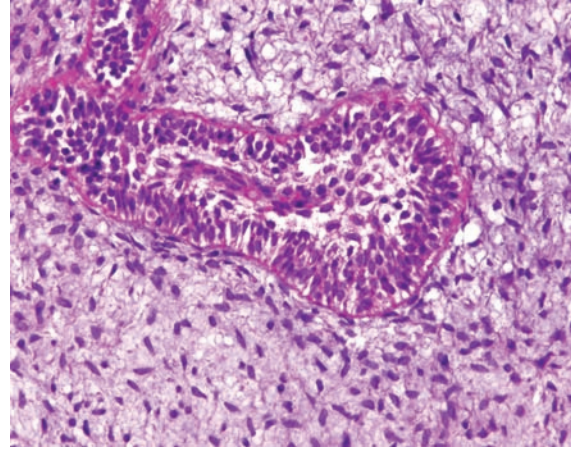
- Hyperplastic dental follicle
- Ameloblastic fibro-odontoma
- Ameloblastic fibrosarcoma



## Ameloblastic Fibroma



A



B

**FIGURE 5-5** *Ameloblastic Fibroma*

**A.** Slender cords of ameloblasts are set in an abundant moderately cellular myxoid stroma. **B.** Epithelial cord is sharply separated by a well-defined basement membrane from the stroma whose spindle and stellate cells are uniformly small with long thin cytoplasmic processes.

### Calcifying Epithelial Odontogenic (Pindborg) Tumor

#### DEFINITION:

An epithelial odontogenic neoplasm characterized by the formation of calcific deposits and amyloid material.

#### CLINICAL FEATURES:

- Broad age range, x = 40 years.; no gender predilection
- Fifty percent associated with impacted tooth; 2/3<sup>rd</sup>s affect the mandible
- Slowly-enlarging jaw mass, usually painless
- Peripheral variant: extraosseous, usually arises in gingiva
- Plain X-ray: circumscribed, radiolucent, uni- or multilocular with flecks of calcification; associated with unerupted tooth

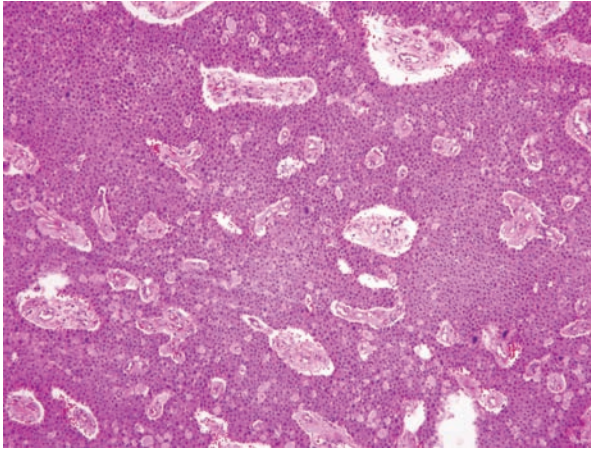
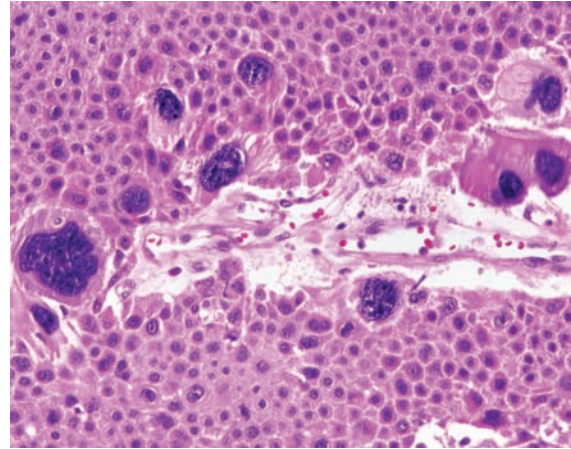
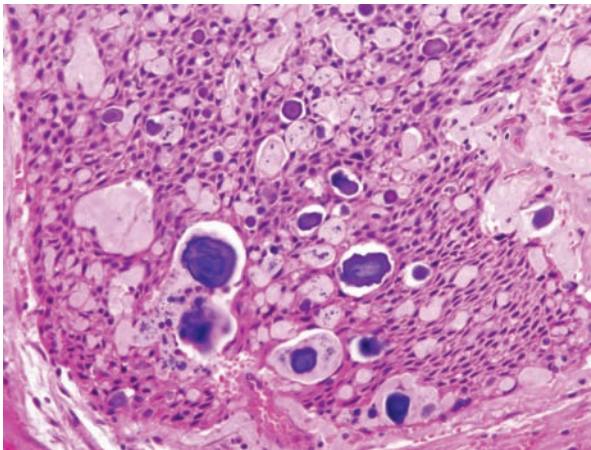
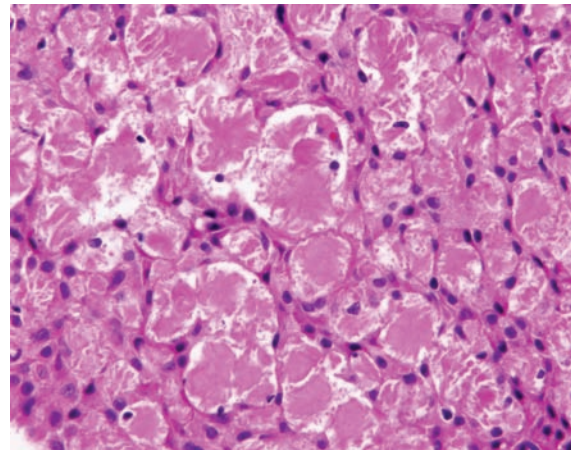
#### GROSS AND HISTOLOGIC FINDINGS:

- Gross: nonspecific soft fragments with gritty calcifications
- Sheets and irregularly contoured islands of large polygonal cells with randomly scattered marked anisonucleosis and hyperchromasia; moderate-abundant eosinophilic cytoplasm with intercellular bridges
- Liesegang ring-like calcific deposits, cribriform foci of hyalinized amyloid-like deposition, and absence of mitotic figures (**Figure 5-6**)
- Focal clear cell change possible
- Positive IHC: pan-cytokeratin staining, Congo-red in amyloid foci

#### DIFFERENTIAL DIAGNOSIS:

- Intraosseous squamous cell carcinoma
- Odontogenic carcinoma

## Calcifying Epithelial Odontogenic (Pindborg) Tumor

**A****B****C****D**

**FIGURE 5-6** *Pindborg Tumor*

**A.** Small vessels punctuate a solid sheet of intensely eosinophilic cells mimicking incomplete squamous differentiation. **B.** Extreme nucleomegaly and hyperchromasia in this focus. Note the absence of mitoses. **C.** Lamellar basophilic Liesegang ring-like calcific deposits vary in diameter. **D.** Amyloid deposition in this image has a cribriform appearance.

### Keratocystic Odontogenic Tumor (Odontogenic Keratocyst)

#### DEFINITION:

A developmental cyst in the tooth-bearing area composed of a benign parakeratotic squamous epithelium 5–9 layers thick that has the potential for recurrence and local infiltration. Only the form with parakeratosis is considered a keratocystic odontogenic tumor, while the orthokeratinizing form is referred to as “orthokeratinizing odontogenic keratocyst.” This latter, much less common variant is not considered here.

#### CLINICAL FEATURES:

- M:F = 1.5:1, children → elderly
- Multiple lesions suggestive of nevoid-basal cell carcinoma (Gorlin) syndrome
- Typically located in the crown of impacted teeth or at the root apex; mandible more common than maxilla; may be seen with an erupted tooth
- Asymptomatic or jaw pain
- Plain X-ray: mainly solitary, radiolucent unilocular or multilocular, not diagnostic

#### GROSS AND HISTOLOGIC FINDINGS:

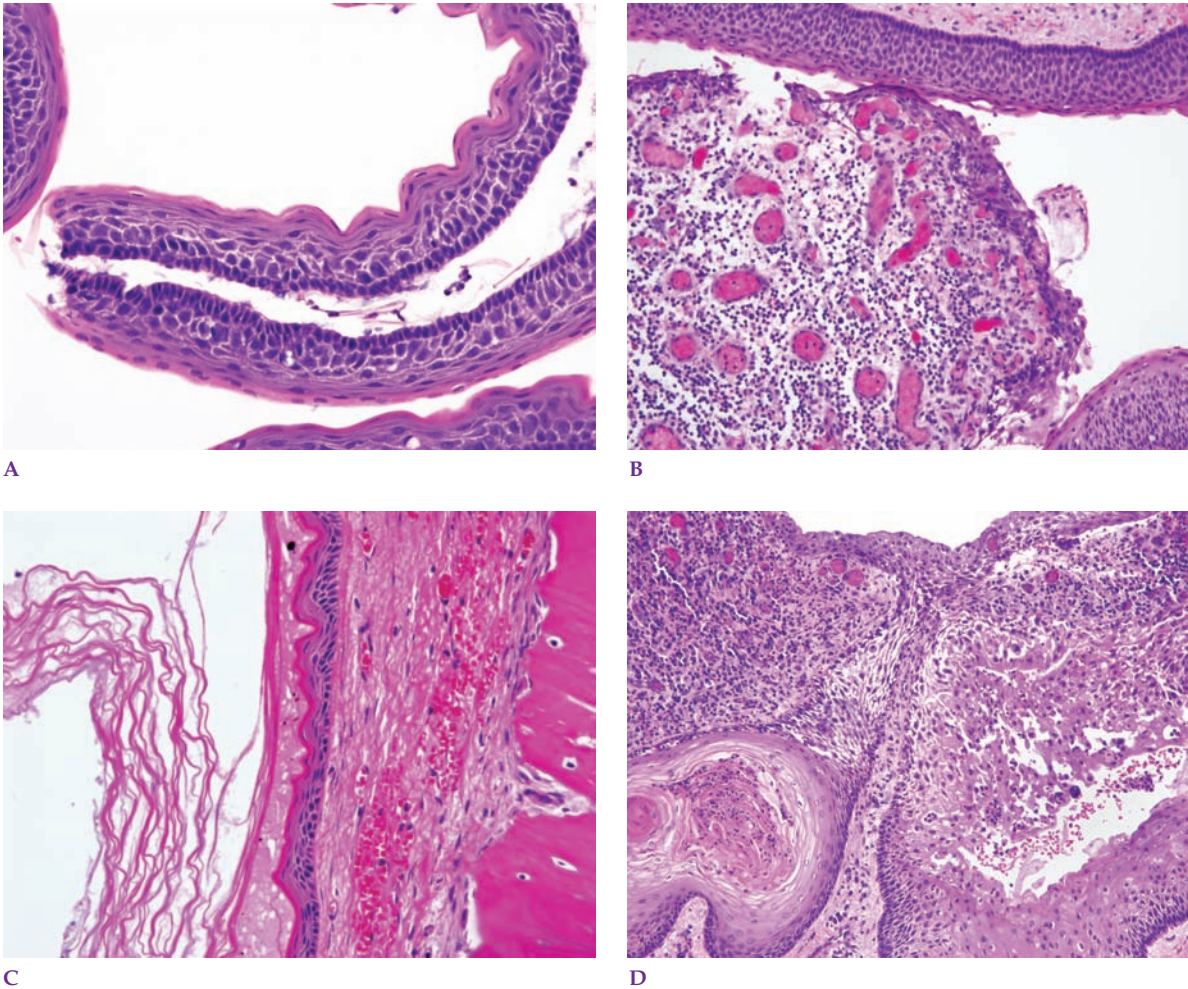
- Gross: nonspecific soft and bony tissue fragments
- Benign squamous epithelium (5–9 cell layers) has a thin corrugated parakeratotic layer and perpendicularly palisading of cells in the basal layer; multiple “daughter” cysts possible (**Figure 5-7**)
- Detachment of cyst epithelium not uncommon; secondary inflammation and pseudoepitheliomatous hyperplasia possible
- Rete ridges usually absent; cysts filled with keratin
- Positive IHC: not applicable for diagnosis

#### DIFFERENTIAL DIAGNOSIS:

- Unicystic ameloblastoma
- Any epithelial-lined cyst of the jaw



## Keratocystic Odontogenic Tumor (Odontogenic Keratocyst)



**FIGURE 5-7** *Odontogenic Keratocyst*

**A.** Detached epithelial strips display a corrugated parakeratotic surface and discrete basal cell palisading. **B.** A focus of inflammation, granulation tissue leads to loss of the parakeratotic layer and mimics an inflammatory odontogenic cyst. **C.** Lamellated keratin desquamates into cyst lumen (*left*) as the cyst erodes bone (*right*). **D.** A patient with Gorlin syndrome shows an inflamed keratocyst with pseudoepitheliomatous hyperplasia. Transformation to squamous carcinoma is rare.

### Odontogenic Myxoma

#### DEFINITION:

A benign intraosseous neoplasm composed of spindle and stellate-shaped cells in a myxomatous matrix.

#### CLINICAL FEATURES:

- Sixty percent in decades 2 to 3 of life; slight female predominance
- Asymptomatic or painless swelling of jaw; 70% arise in the mandible
- Plain X-ray: radiolucent, uni- or multilocular, usually sharply demarcated borders; similar to ameloblastoma

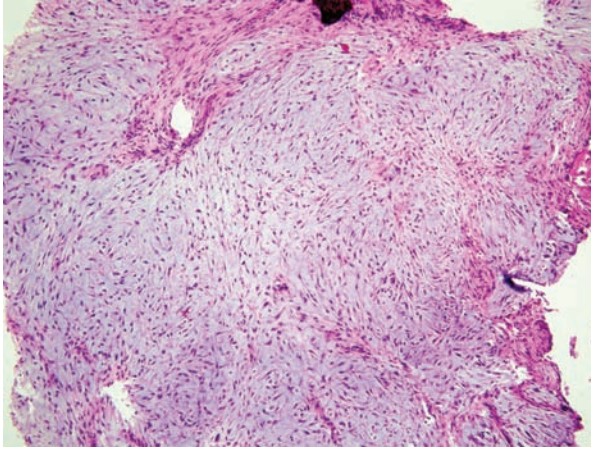
#### GROSS AND HISTOLOGIC FINDINGS:

- Gross: soft, grey, glistening gelatinous mass
- An ample myxoid stroma contains a variable (usually low) number of randomly scattered cytologically banal small stellate and spindle-shaped cells; an absence of necrosis, and minimal vascularity (**Figure 5-8**)
- Myxofibroma: term applied with increasing collagen deposition
- Rarely, odontogenic nests are seen
- Positive IHC: vimentin, Alcian blue (matrix); negative staining with epithelial markers

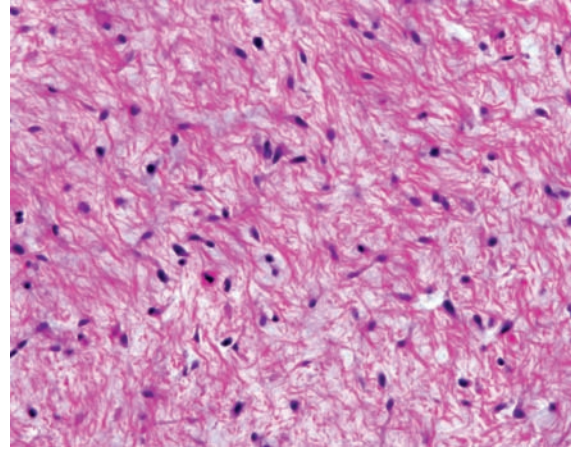
#### DIFFERENTIAL DIAGNOSIS:

- Hyperplastic dental follicle
- Ameloblastic fibroma
- Myxoid sarcoma

## Odontogenic Myxoma



A



B

**FIGURE 5-8** *Odontogenic Myxoma*

**A.** Myxoid stroma is moderately cellular and lacks epithelial structures. **B.** This example contains an abundance of collagen and is more accurately considered a fibromyxoma.

### Odontoma, Complex Type

#### DEFINITION:

A benign lesion, considered hamartomatous by many, that consists of mineralized cementum-like material, dentin, and enamel in a haphazard arrangement. Odontoma is the most common of all odontogenic mass lesions. The *compound* type of odontoma resembles a tooth and is not discussed here.

#### CLINICAL FEATURES:

- Children—young adults; M:F = 2:1
- Arise in posterior mandible; painless, slow-growing mass
- Plain X-ray: radio-opaque with a radiolucent border or a radiolucent mass; associated with impacted teeth, usually third molar

#### GROSS AND HISTOLOGIC FINDINGS:

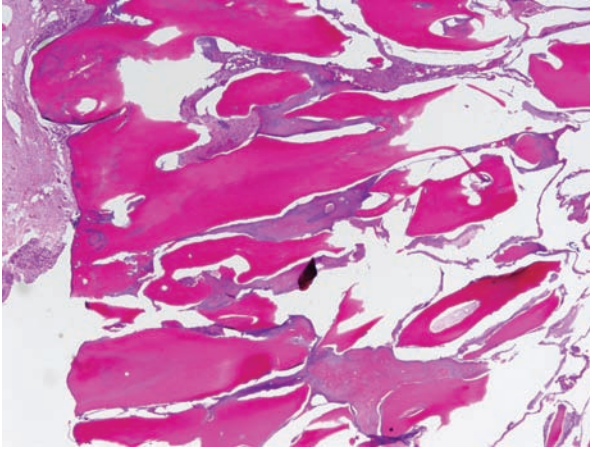
- Gross: nonspecific hard, yellow-white calcified tissue fragments
- Haphazard mixture of dentin, enamel, with smaller amounts of cementum-like material and pulp; loose connective tissue possible (**Figure 5-9**)
- Positive IHC: not applicable for diagnosis

#### DIFFERENTIAL DIAGNOSIS:

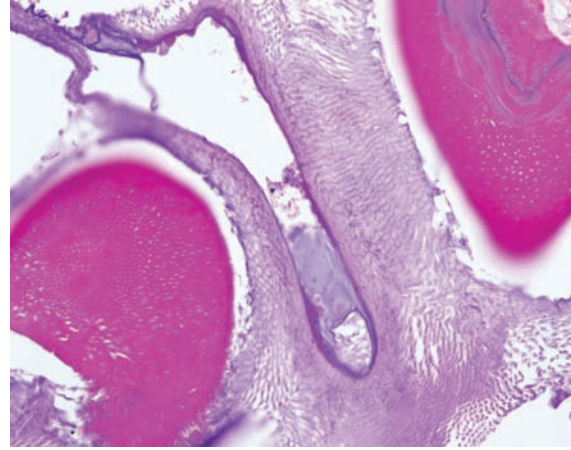
- Normal tooth
- Ameloblastic fibro-odontoma



## Odontoma, Complex Type



A



B

**FIGURE 5-9** *Odontoma, Complex Type*

**A.** Brightly acidophilic dentin and enamel are haphazardly mixed together with no semblance of a tooth. **B.** Ridge-like structure of enamel contrasts with acidophilic dentin demonstrating dentinal tubules.

### Craniofacial Osteosarcoma, Conventional Type

#### DEFINITION:

An osteoid or bone-producing sarcoma.

#### CLINICAL FEATURES:

- M:F = 2:1; peak in decades 4 to 5 of life
- Mandible slightly more commonly affected than maxilla
- Painful/painless mass, diplopia, loosening of teeth; associated with Paget's disease, prior radiation therapy
- Plain X-ray: destructive lytic or sclerotic lesion, "sunburst" pattern produced by periosteal elevation

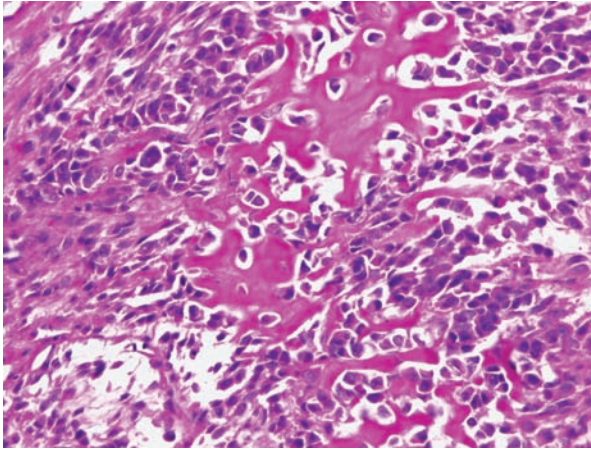
#### GROSS AND HISTOLOGIC FINDINGS:

- Gross: hard calcified fragments; also white, cartilaginous grey-blue cut surface
- Highly cellular tissue containing markedly hyperchromatic spindle and pleomorphic cells with irregular nuclear contours, easily found mitoses, and variable amount of malignant osteoid (lace-like dense hyalinized strands enveloping individual cells and cell clusters); high percentage show hypercellular cartilaginous lobules mimicking chondrosarcoma (**Figure 5-10**)
- Variable number of osteoclastic giant cells, often absent
- Positive IHC: not applicable for diagnosis

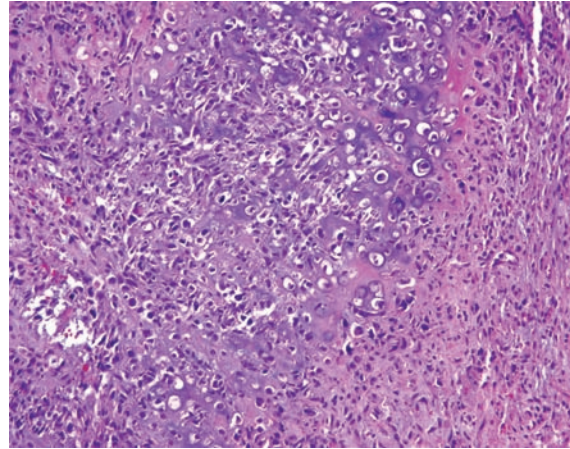
#### DIFFERENTIAL DIAGNOSIS:

- Chondrosarcoma
- Osteblastoma

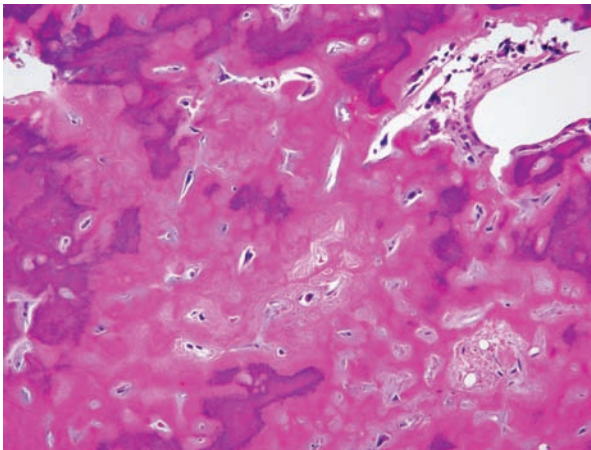
## Craniofacial Osteosarcoma, Conventional Type



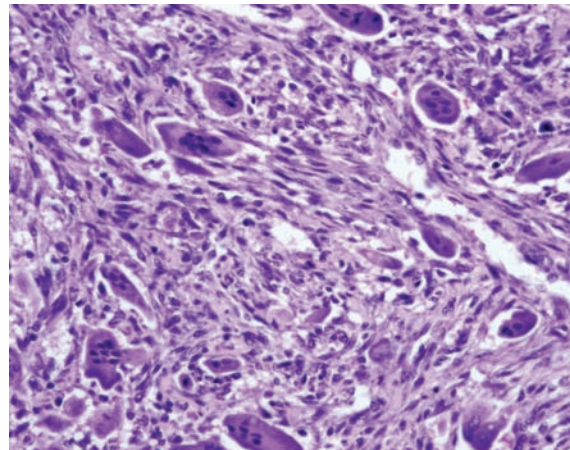
A



B



C



D

**FIGURE 5-10** *Osteosarcoma, Conventional Type*

**A.** Classic appearance of lacy “malignant osteoid” enveloping malignant polygonal cells. **B.** Lobule of cartilaginous differentiation. **C.** An intensely sclerotic focus mimicking benign bone; malignant cells at *top right*. **D.** Fibroblastic variant shows many osteoclastic giant cells. Small amounts of osteoid were present elsewhere in this tissue.





## Ear

### NONNEOPLASTIC LESIONS

KELOID

CHONDRODERMATITIS NODULARIS CHRONICUS HELICIS

CHOLESTEATOMA

CHOLESTEROL GRANULOMA

### BENIGN NEOPLASMS

LANGERHANS CELL HISTIOCYTOSIS

JUGULOTYMPANIC PARAGANGLIOMA

MIDDLE EAR MENINGIOMA

CERUMINOUS ADENOMA

MIDDLE EAR ADENOMA

VESTIBULAR SCHWANNOMA (ACOUSTIC NEUROMA)

ENDOLYMPHATIC SAC PAPILLARY TUMOR (HEFFNER TUMOR)

### Keloid

#### DEFINITION:

Excessive deposition of collagen leading to a scar that extends beyond the borders of the original wound.

#### CLINICAL FEATURES:

- Any age, most common in decades 2 to 3
- Nonwhites more often affected
- Commonly affected sites: earlobe, pinna, cheek, arm

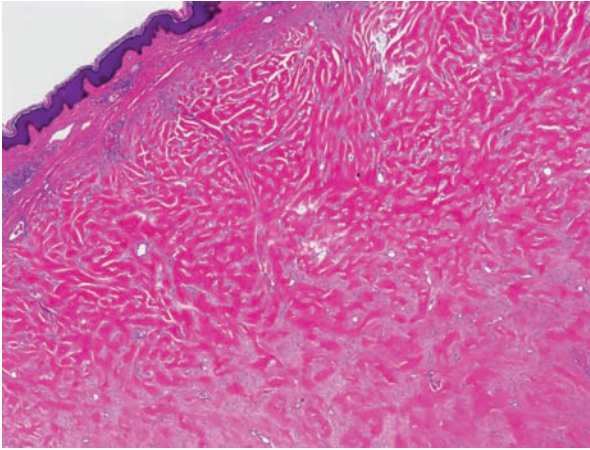
#### GROSS AND HISTOLOGIC FINDINGS:

- Gross: firm, raised plaque or nodule well-demarcated from surrounding skin
- Thick, eosinophilic bundles of dermal collagen in haphazardly arranged and in nodular aggregates; extremely low cellularity and minimal vascularity (**Figure 6-1**)
- Epidermal atrophy and loss of adnexal structures; may be secondarily ulcerated
- Positive IHC: not applicable for diagnosis

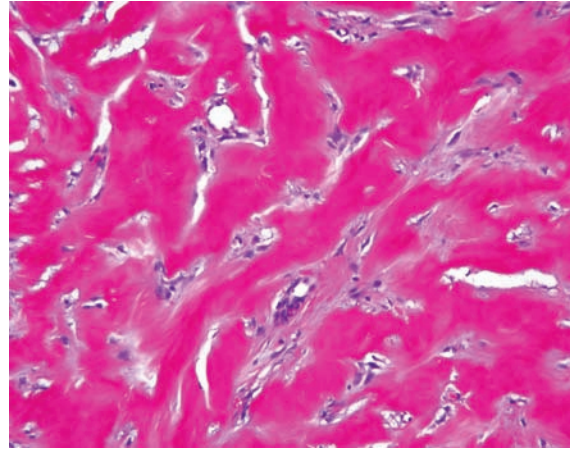
#### DIFFERENTIAL DIAGNOSIS:

- Hypertrophic scar
- Dermatofibroma

## Keloid



A



B

**FIGURE 6-1** *Keloid*

**A.** This circumscribed dermal nodule contains thick brightly eosinophilic collagen fibers. **B.** Few fibroblasts and capillaries separate thickened collagen bands.

### Chondrodermatitis Nodularis Chronicus Helicis

#### DEFINITION:

Nonneoplastic ulcerative transepidermal inflammatory disorder of the external ear.

#### CLINICAL FEATURES:

- Middle age → elderly; male predominance
- Intensely painful nodule; most common at apex of the helix, less often antihelix, tragus

#### GROSS AND HISTOLOGIC FINDINGS:

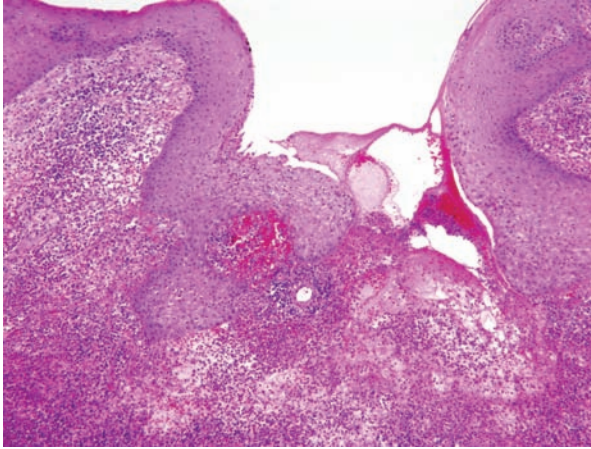
- Gross: <1 cm dome-shaped nodule; sometimes has a depressed central umbilication
- Epidermal hyperplasia with crater-like ulcer, scale crust, granulation tissue; fibrosis involving perichondrium and cartilage and focal dropout of chondrocytes (**Figure 6-2**)
- Mixed inflammatory infiltrate; fibrin deposition at ulcer base
- Positive IHC: not applicable for diagnosis

#### DIFFERENTIAL DIAGNOSIS:

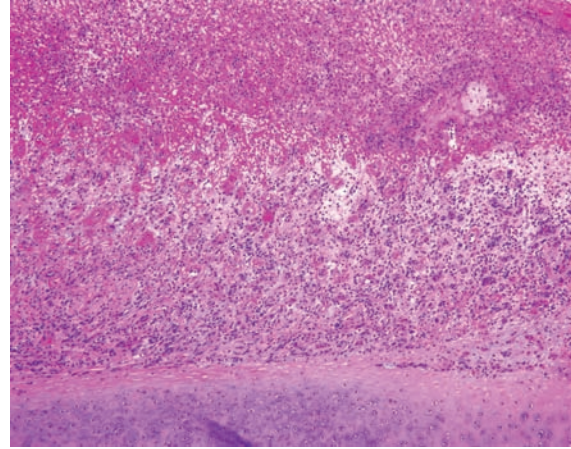
- Relapsing polychondritis
- Squamous cell carcinoma



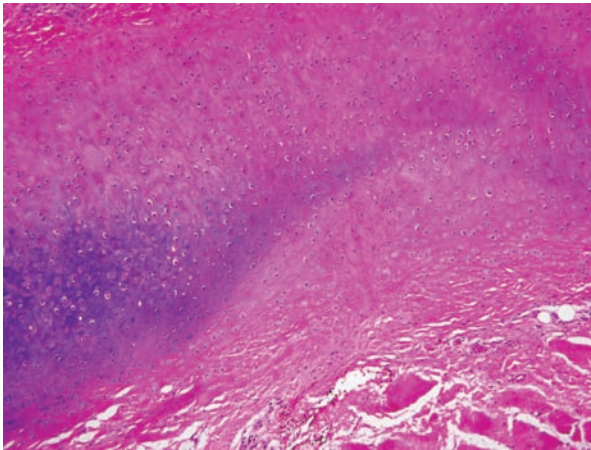
## Chondrodermatitis Nodularis Chronicus Helicis



A



B



C

**FIGURE 6-2** *Chondrodermatitis Nodularis Chronicus Helicis*

**A.** Central umbilicated cutaneous ulcer. **B.** Acute inflammation and granulation tissue extend to the perichondrium and cartilage (*bottom*). **C.** Focal loss of basophilia within chondroid matrix.

### Cholesteatoma

#### DEFINITION:

Invasive proliferation of benign keratinizing squamous epithelium within the middle ear and mastoid associated with accumulation of masses of keratinous debris. Occurs in both acquired and congenital forms.

#### CLINICAL FEATURES:

- Wide age range; no gender preference
- Otolgia, hearing loss, otorrhea
- Associated with repeated bouts of otitis media

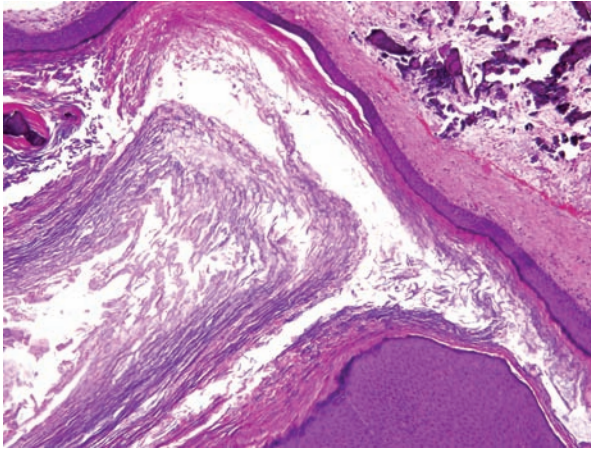
#### GROSS AND HISTOLOGIC FINDINGS:

- Gross: gray-white mass of keratin and pink tissue; sometimes an intact cyst is received
- Benign appearing keratinizing squamous epithelium (often detached) with distinct granular layer and lacking cutaneous adnexa; variable inflammatory infiltrate, cyst rupture leads to foreign body giant cell reaction, keratin-induced granulomas (**Figure 6-3**)
- Positive IHC: not applicable for diagnosis

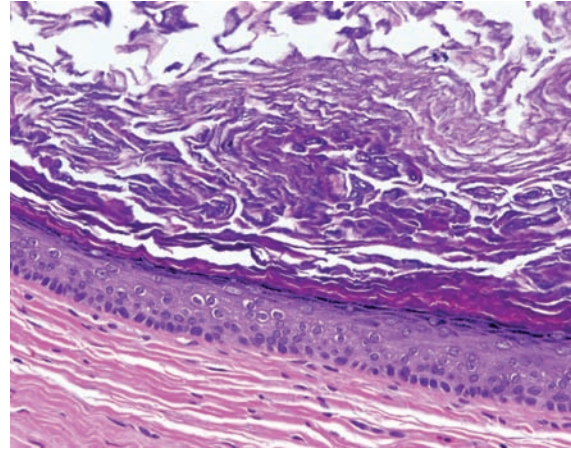
#### DIFFERENTIAL DIAGNOSIS:

- Cholesterol granuloma

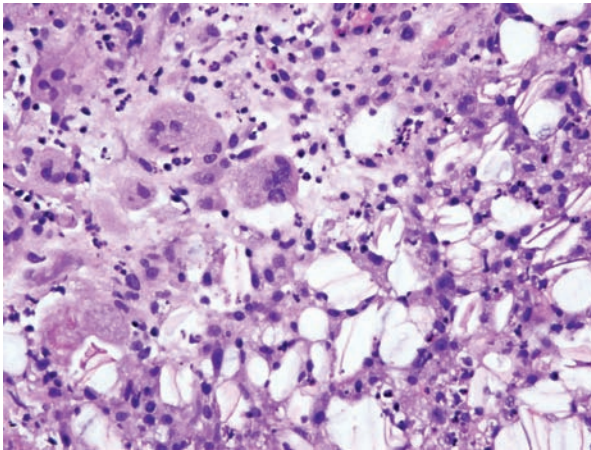
## Cholesteatoma



A



B



C

**FIGURE 6-3** *Cholesteatoma*

**A.** Laminated stacks of luminal-based squames are surrounded by keratinizing squamous epithelium. Fragments of undecalcified bone are at upper right.

**B.** Bland squamous cells are surfaced by an obvious basophilic granular layer.

**C.** Keratin Granuloma. Flakes of anucleated squames induce an inflammatory response with several foreign body-type giant cells (*left*).

### Cholesterol Granuloma

#### DEFINITION:

Stromal inflammatory reaction secondary to deposition of cholesterol crystals and by-products of hemoglobin degradation in the middle ear and mastoid that fails to resorb. Not related to cholesteatoma.

#### CLINICAL FEATURES:

- Any age; no gender preference
- Hearing loss; tinnitus, vertigo, otorrhea; associated with repeated bouts of otitis media
- Blue or black tympanic membrane secondary to bloody effusion

#### GROSS AND HISTOLOGIC FINDINGS:

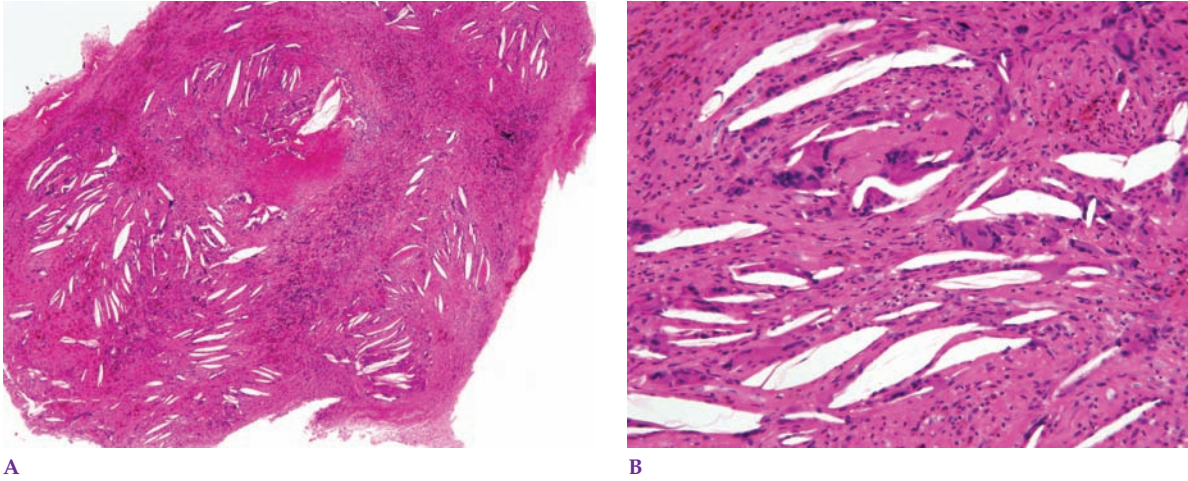
- Gross: hemorrhagic and brownish friable soft tissue fragments
- Acicular cholesterol clefts associated with chronic granulation tissue, hemosiderin-filled macrophages, and multinucleated foreign body giant cells (**Figure 6-4**)
- May exist simultaneously with cholesteatoma
- Positive IHC: not applicable for diagnosis

#### DIFFERENTIAL DIAGNOSIS:

- Cholesteatoma
- Langerhans cell histiocytosis



## Cholesterol Granuloma



**FIGURE 6-4** *Cholesterol Granuloma*

**A.** Many cholesterol cleft spaces are scattered in this fibrous granulation tissue; brownish hemosiderin deposition is at the *right of center*. **B.** Bipolar tapering of cholesterol clefts and partial engulfment by foreign body giant cell reaction.



### Langerhans Cell Histiocytosis

#### DEFINITION:

Neoplastic proliferation of Langerhans cells characterized by cells containing ultra-structural Birbeck granules and expressing CD1a, langerin, and S-100 protein.

#### CLINICAL FEATURES:

- May be unifocal or part of multisystem disease
- Infants → adolescents; slight male predominance
- Otalgia, tinnitus, otitis media, unilateral hearing loss

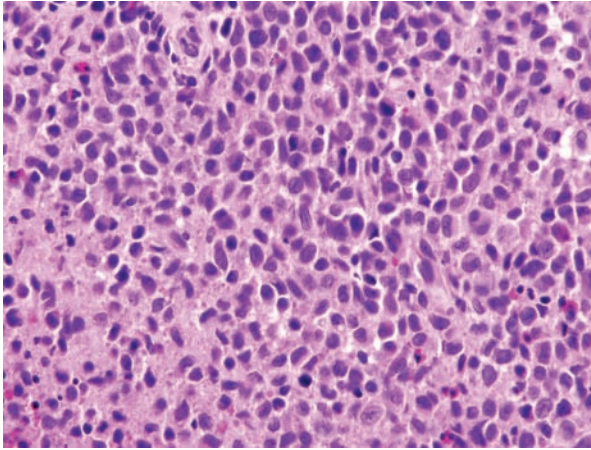
#### GROSS AND HISTOLOGIC FINDINGS:

- Gross: nonspecific tan-pink fragments of tissue
- Infiltration by intermediate-sized histiocytes having distinctive multilobulated, folded, and grooved nuclei (some with a “coffee-bean” appearance) and a small amount of eosinophilic cytoplasm; variable population of eosinophils accompany histiocytes (**Figure 6-5**)
- Some histiocytes are binucleated; eosinophilic abscesses, Charcot-Leyden crystals possible
- Positive IHC: langerin, S-100, CD1a, CD68

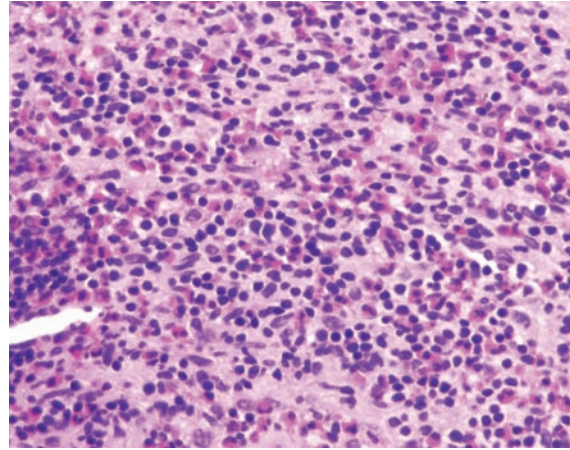
#### DIFFERENTIAL DIAGNOSIS:

- Rosai-Dorfman disease
- Chronic osteomyelitis
- Malignant lymphoma

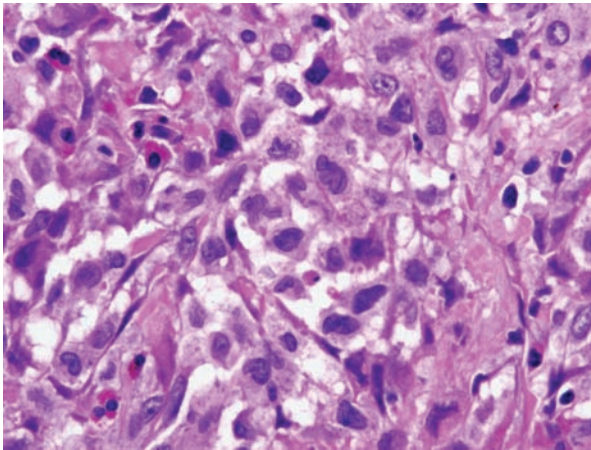
## Langerhans Cell Histiocytosis



A



B



C

**FIGURE 6-5** *Langerhans Cell Histiocytosis*

**A.** Solid sheet of histiocytic cells with few eosinophils. **B.** Numerous eosinophils and lymphocytes obscure Langerhans cells. **C.** Convoluted almost cerebriform nuclei with occasional linear grooves are seen.

### Jugulotympanic Paraganglioma

#### DEFINITION:

Neoplasm arising from paraganglia located in the middle ear.

#### CLINICAL FEATURES:

- Decades 5 to 6 of life; female predominance
- Tinnitus, conductive hearing loss, otalgia, vertigo, facial palsy, bone erosion on plain X-ray

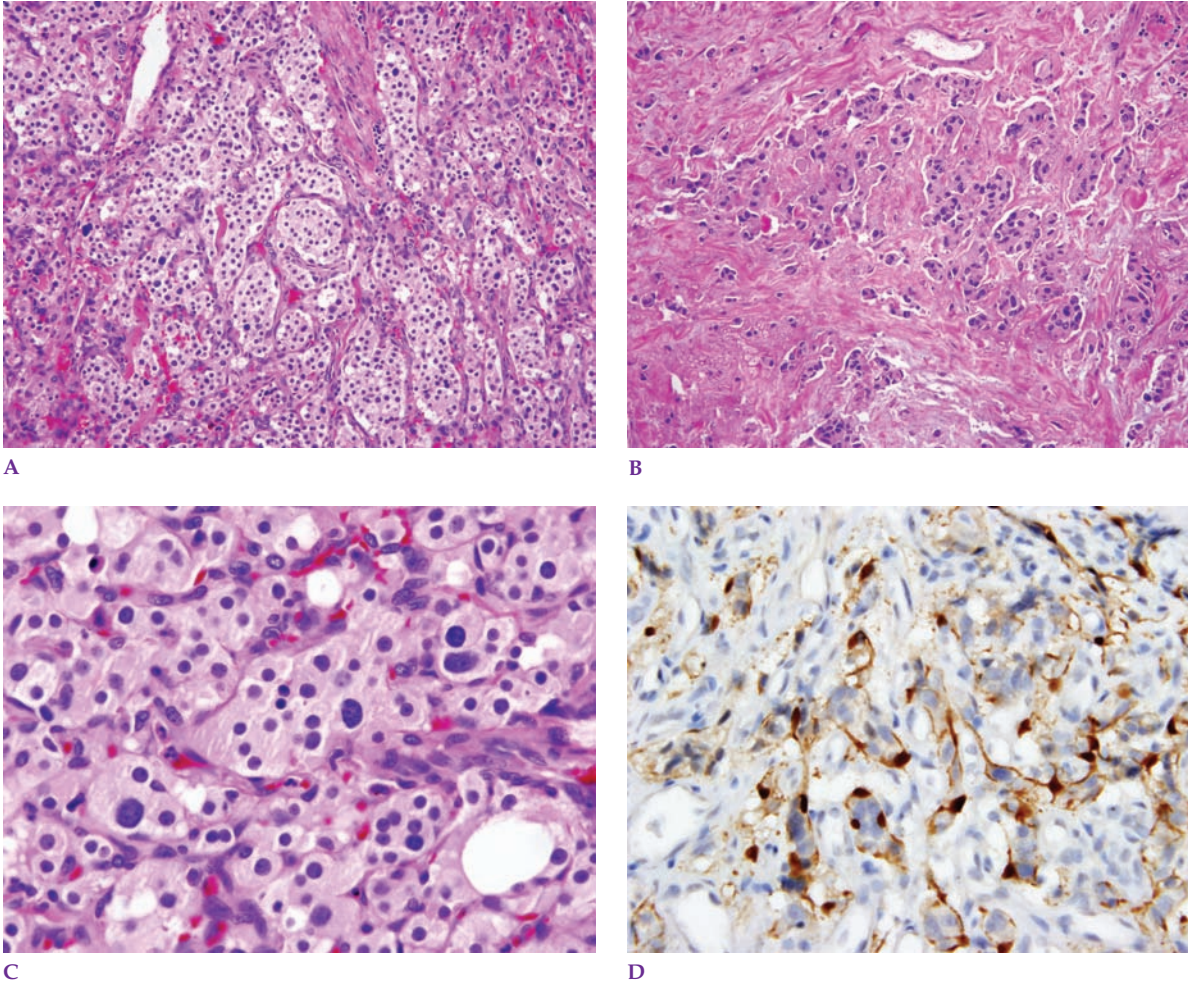
#### GROSS AND HISTOLOGIC FINDINGS:

- Gross: nonspecific pink-tan fragments soft tissue lacking a fibrous capsule, sometimes hemorrhagic; often with associated bone fragments
- Proliferation of epithelioid cells in a vascular stroma with a characteristic syncytial nested (so-called “zellballen”) pattern created by an anastomosing network of congested fibrovascular septa
- Cells have a moderate amount of granular eosinophilic cytoplasm with scattered anisonucleosis characterized by nucleomegaly, pleomorphism, and hyperchromasia (**Figure 6-6**)
- Sustentacular cells surround cell nests, but poorly visualized with H&E stain
- Variable amount of sclerosis, crushed cells, and dilated vessels; few mitoses
- Positive IHC: chief cells positive for synaptophysin, chromogranin, CD56, and S-100 positive sustentacular cells; negative pan-cytokeratin stains

#### DIFFERENTIAL DIAGNOSIS:

- Middle ear adenoma
- Meningioma
- Metastatic renal cell carcinoma

## Jugulotympanic Paraganglioma



**FIGURE 6-6** *Jugulotympanic Paraganglioma*

**A.** Nested “zellballen” architecture created by numerous anastomosing vessels. **B.** Sclerosing variant shows cells in small clusters with an infiltrative appearance. **C.** Scattered nucleomegaly and hyperchromasia are apparent. **D.** S-100 stain highlights sustentacular cells with long cytoplasmic processes partially surrounding cells nests.



### Middle Ear Meningioma

#### DEFINITION:

Benign neoplasm derived from meningotheelial cells and usually arising from the dura mater. In the middle ear, most examples represent extension from an intracranial tumor.

#### CLINICAL FEATURES:

- Broad age range from children to elderly; peak in decade 6
- F:M = 2:1
- Tinnitus, headache, hearing loss, chronic otitis media, otalgia, vertigo

#### GROSS AND HISTOLOGIC FINDINGS:

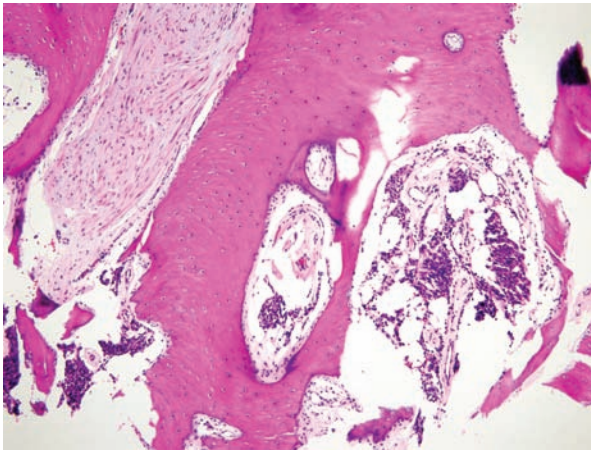
- Gross: whitish soft tissue and gritty fragments
- Syncytia of epithelioid cells with rounded, uniform nuclei, moderate amount of eosinophilic cytoplasm, and indistinct cell borders exhibiting a lobular whorled pattern; intranuclear cytoplasmic pseudoinclusions and psammoma bodies possible, but mitoses rare (**Figure 6-7**)
- Positive IHC: EMA, vimentin, S-100 (focal); negative staining with synaptophysin, cytokeratin, and chromogranin

#### DIFFERENTIAL DIAGNOSIS:

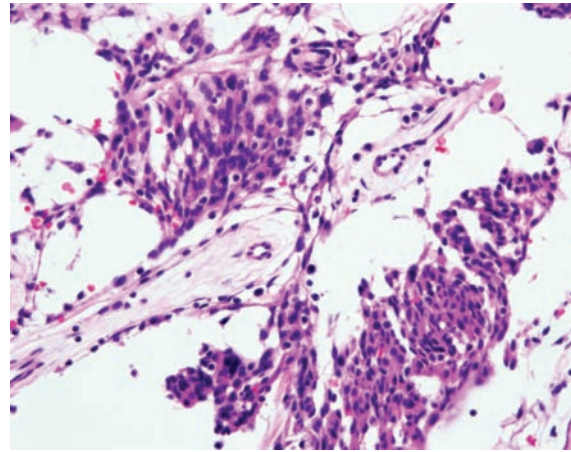
- Paraganglioma
- Schwannoma



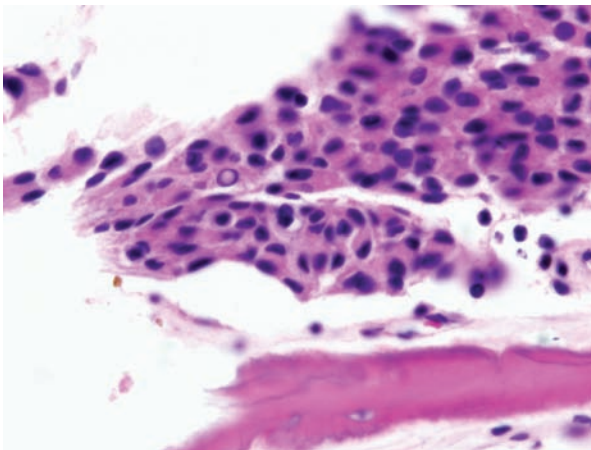
## Middle Ear Meningioma



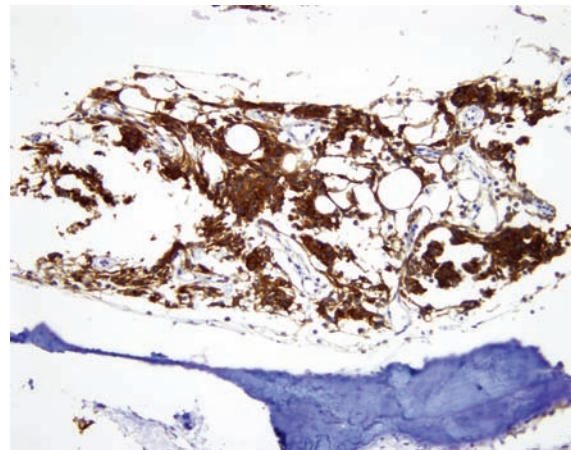
A



B



C



D

**FIGURE 6-7** *Middle Ear Meningioma*

**A.** Irregularly contoured cell nests are embedded within mastoid bone. **B.** Vaguely lobulated nests of uniformly-sized cells with a moderate amount of cytoplasm.

**C.** Intranuclear cytoplasmic inclusions are infrequent. **D.** Intense cytoplasmic staining with EMA.

### Ceruminous Adenoma

#### DEFINITION:

Benign tumor composed of apocrine cerumen-forming glands with a myoepithelial layer arising in the *external* ear.

#### CLINICAL FEATURES:

- Decades 5 to 6; M = F
- Painless, with or without hearing loss

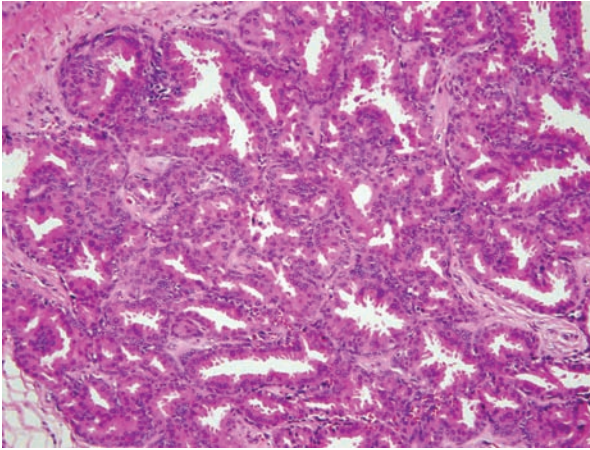
#### GROSS AND HISTOLOGIC FINDINGS:

- Gross: polypoid mass; pink-tan cut surface
- Circumscribed, nonencapsulated glandular proliferation (variably cystic) often in a back-to-back, but not cribriform, arrangement; dual inner epithelial layer (commonly apocrine/oncocyctic with decapitated apocrine snouts), and an outer myoepithelial cell population (**Figure 6-8**)
- Luminal cells may contain yellowish cytoplasmic cerumen (ceroid) pigment; absence of infiltrative growth, nuclear pleomorphism, and necrosis
- Positive IHC: pan-cytokeratin, CK 7 in luminal cells, and myoepithelial markers (p63, S-100) in abluminal/myoepithelial cells

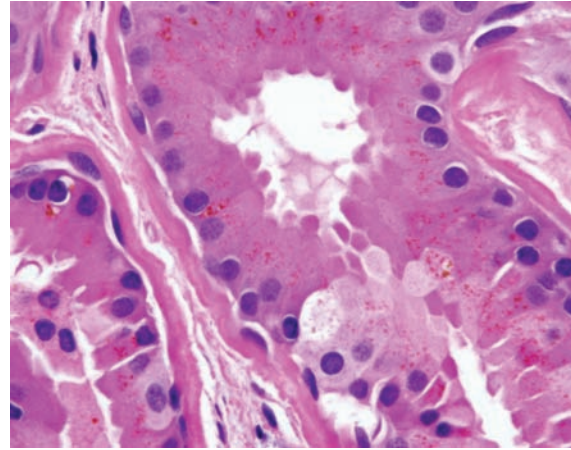
#### DIFFERENTIAL DIAGNOSIS:

- Middle ear adenoma
- Paraganglioma
- Ceruminous adenocarcinoma

## Ceruminous Adenoma



A



B

**FIGURE 6-8** *Ceruminous Gland Adenoma*

**A.** Back-to-back glandular proliferation with a circumscribed, but nonencapsulated periphery. **B.** Cells having abundant eosinophilic cytoplasm show apocrine type decapitation. Brownish ceroid pigment is present.

### Middle Ear Adenoma

#### DEFINITION:

Benign glandular neoplasm of the middle ear that demonstrates neuroendocrine differentiation.

#### CLINICAL FEATURES:

- Broad age range, peak decade 5; no gender preference
- Hearing loss, tinnitus, headache, facial nerve palsy, “fullness” in the ear

#### GROSS AND HISTOLOGIC FINDINGS:

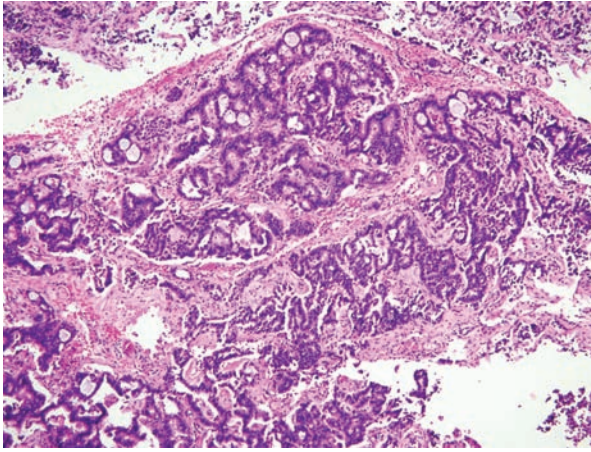
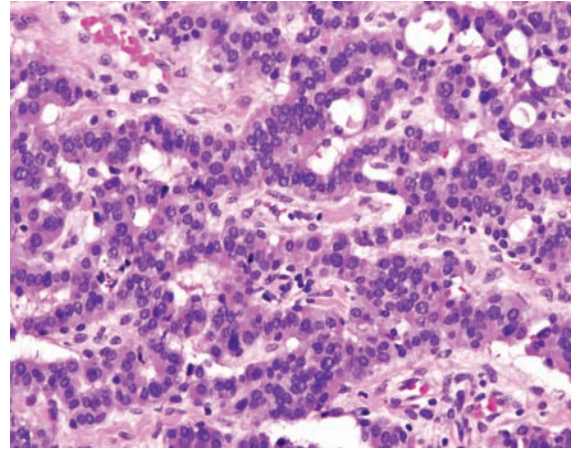
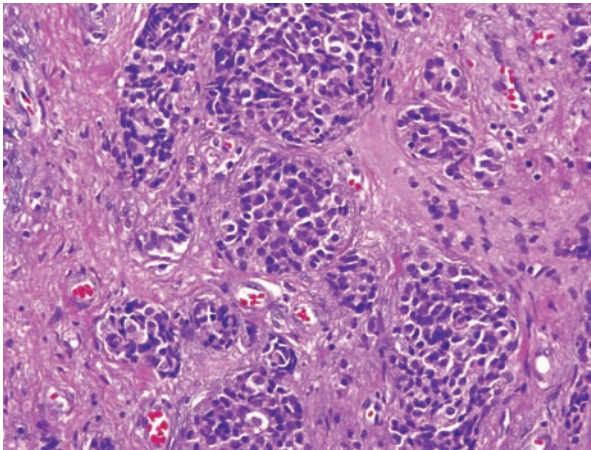
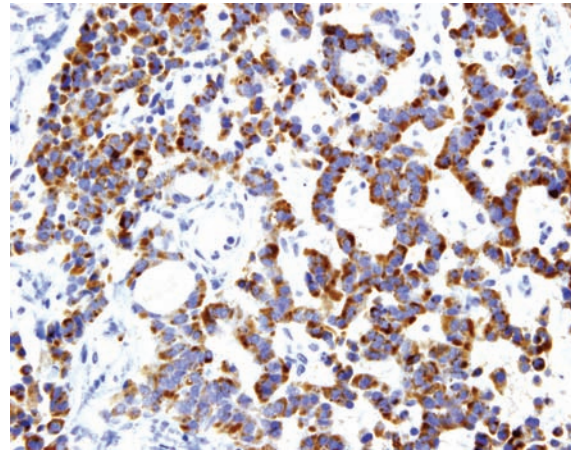
- Gross: unencapsulated pale gray to tan-brown tissue fragments
- Back-to-back glandular, solid, and ribbon-like pattern of isomorphic plasmacytoid-appearing cells having modest amounts of eosinophilic cytoplasm, eccentric round to oval nuclei without nucleoli; some degree of anisonucleosis (**Figure 6-9**)
- Dual layer of luminal and abluminal cells; mitoses rare to absent
- Positive IHC: CD56, chromogranin, synaptophysin, pan-cytokeratin, cytokeratin 7

#### DIFFERENTIAL DIAGNOSIS:

- Ceruminous adenoma
- Paraganglioma



## Middle Ear Adenoma

**A****B****C****D**

**FIGURE 6-9** *Middle Ear Adenoma*

**A.** Back-to-back glands and ribbon-like cords of cells are seen. **B.** Isomorphic cuboidal cells are in thin linear strands. **C.** Nests of solid cells imitate the insular pattern of well-differentiated neuroendocrine carcinoma (carcinoid). **D.** Chromogranin staining confirms the neuroendocrine nature of this neoplasm.



### Vestibular Schwannoma (Acoustic Neuroma)

#### DEFINITION:

Benign neoplasm of Schwann cells arising from the eighth cranial nerve.

#### CLINICAL FEATURES:

- Peak in decades 5 to 6; F > M
- Most common at cerebellopontine angle
- Vertigo, sensorineural hearing loss, tinnitus
- Bilaterality associated with neurofibromatosis type 2

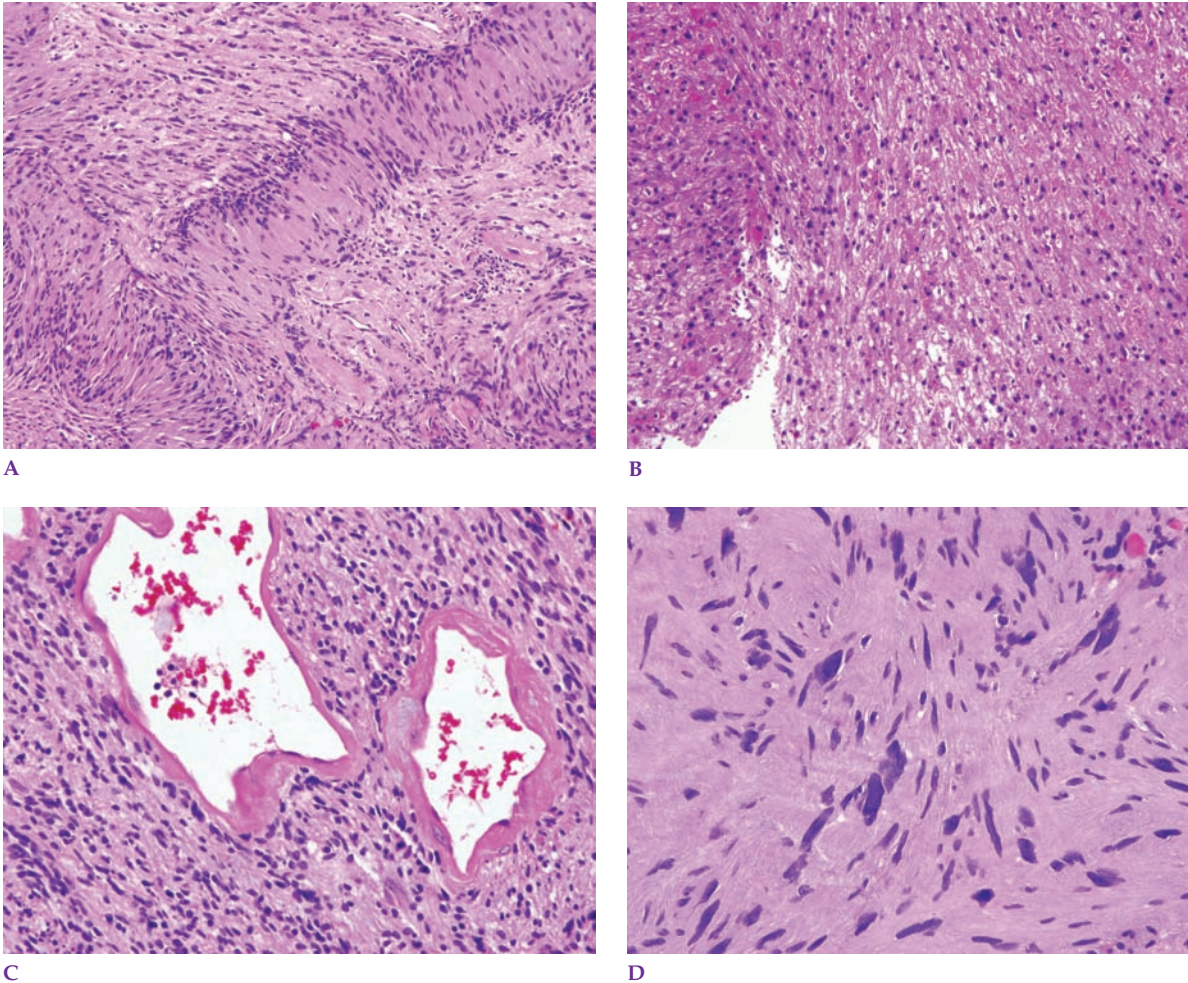
#### GROSS AND HISTOLOGIC FINDINGS:

- Gross: gray-white rubbery tissue, may have cystic change
- Primarily Antoni A histology with syncytial fascicles of spindle cells some with serpiginous nuclear contours and isolated anisonucleosis showing variable nuclear palisading and formation of Verocay bodies; sporadic; Antoni B foci with loose reticular pattern, rounded nuclei with delicate cytoplasmic processes (**Figure 6-10**)
- Variable degree of vascularity with vascular wall hyalinization
- Positive IHC: S-100, vimentin; negative for pan-cytokeratin, EMA

#### DIFFERENTIAL DIAGNOSIS:

- Neurofibroma
- Melanoma
- Meningioma

## Vestibular Schwannoma (Acoustic Neuroma)



**FIGURE 6-10** *Vestibular Schwannoma (Acoustic Neuroma)*

**A.** Highly cellular Antoni A histology with nuclear palisading forming a Verocay body. **B.** Antoni B areas with a loose matrix and rounded cell nuclei. **C.** Vascular wall hyalinization. **D.** Striking nucleomegaly, and nuclear hyperchromasia are considered degenerative phenomena.

### Endolymphatic Sac Papillary Tumor (Heffner Tumor)

#### DEFINITION:

Benign locally aggressive nonmetastasizing papillary epithelial neoplasm in or near the endolymphatic sac of the inner ear.

#### CLINICAL FEATURES:

- Wide age range with peak decades 4 to 5 of life; slight female predominance
- Hearing loss, tinnitus, vertigo, facial nerve palsy
- Bilaterality associated with Von Hippel-Lindau syndrome

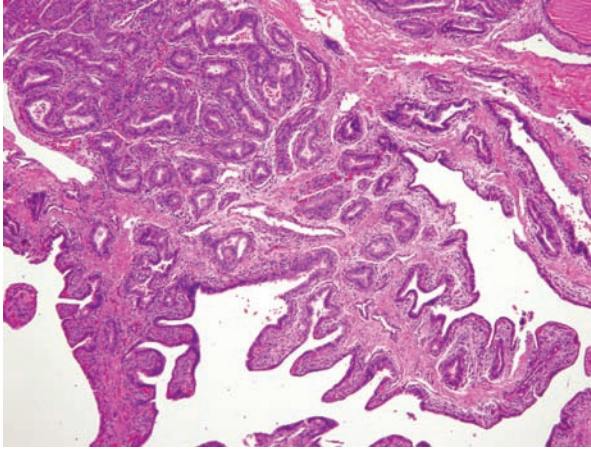
#### GROSS AND HISTOLOGIC FINDINGS:

- Gross: tan-pink soft fragments
- Broad, short papillary projections and thyroidal-like follicular cystic spaces containing eosinophilic colloid-like proteinaceous material; papillae lined by single layer of cuboidal/low columnar cells with bland nuclei (**Figure 6-11**)
- Focal clear cell change; no necrosis or mitoses
- Positive IHC: pan-cytokeratin, EMA (variable), GFAP, S-100; negative for thyroglobulin, TTF-1 synaptophysin

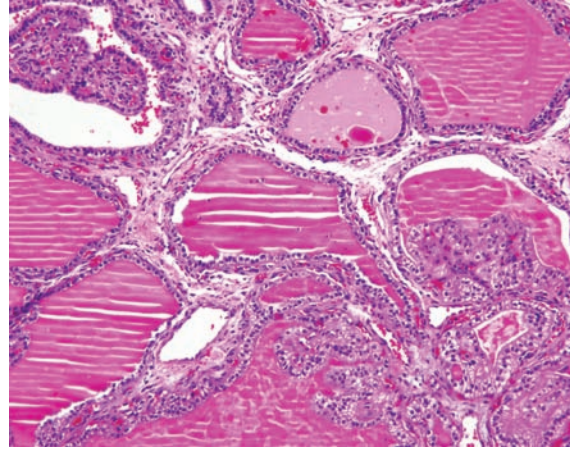
#### DIFFERENTIAL DIAGNOSIS:

- Metastatic papillary thyroid carcinoma
- Choroid plexus papilloma
- Middle ear adenoma

## Endolymphatic Sac Papillary Tumor (Heffner Tumor)



A



B

**FIGURE 6-11** *Endolymphatic Sac Papillary Tumor*

**A.** Short villiform-like papillae and glands. **B.** Dilated glands contain opaque eosinophilic colloid-like material mimicking thyroid follicles.





## Soft Tissue/Miscellaneous

### **NONNEOPLASTIC LESIONS**

BRANCHIAL CLEFT CYST

NODULAR FASCIITIS

### **BENIGN NEOPLASMS**

LYMPHANGIOMA

TERATOMA

FIBROMATOSIS

SPINDLE CELL/PLEOMORPHIC LIPOMA

### Branchial Cleft Cyst

#### DEFINITION:

Cystic and noncystic lesions arising from abnormal development of the branchial apparatus.

#### CLINICAL FEATURES:

- First and second branchial cleft anomalies are most common; 80% to 90% are cysts arising from the second branchial cleft
- First branchial cleft anomalies: occur in and around the ear
- Second branchial cleft anomalies: usually a cyst located just anterior to the sternocleidomastoid muscle/wide age range, peak in decade 4 of life

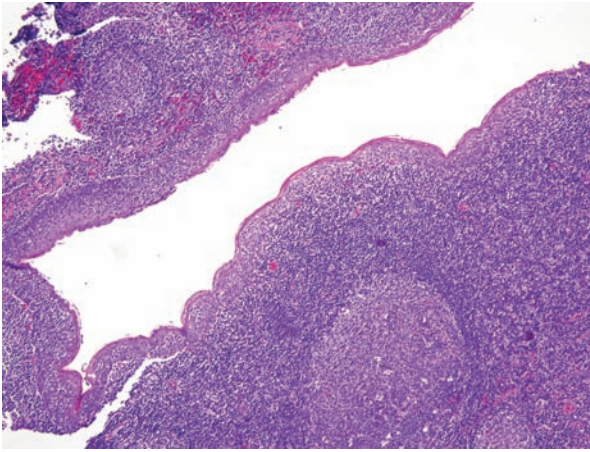
#### GROSS AND HISTOLOGIC FINDINGS:

- Gross: empty or yellowish liquid-filled cyst; skin with sinus tract; fragments of cartilage and soft tissue
- Cyst lined by respiratory or squamous epithelium with or without adnexal structures and often surrounded by a cuff of lymphoid tissue with secondary lymphoid follicle formation; cyst lumen contains nucleated and anucleate squames, macrophages, inflammatory cells (**Figure 7-1**)
- Cyst wall variably fibrotic and contains mixed inflammatory infiltrate
- Sinus tracts composed of mixed inflammatory infiltrate sometimes associated with squamous epithelium; hyaline cartilage seen in first branchial cleft anomaly
- Positive IHC: not applicable for diagnosis

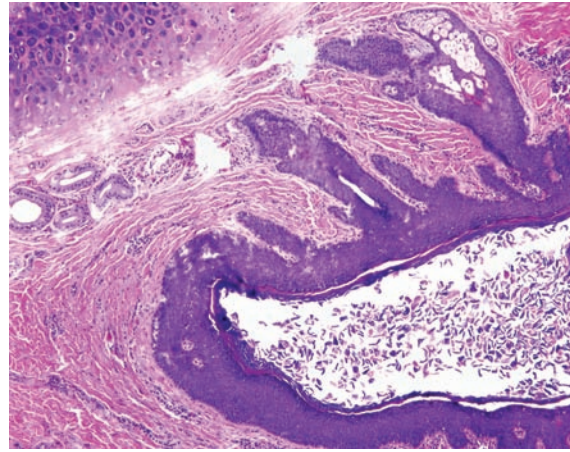
#### DIFFERENTIAL DIAGNOSIS:

- Metastatic cystic squamous carcinoma
- Thyroglossal duct cyst

## Branchial Cleft Cyst



A



B

**FIGURE 7-1** *Branchial Cleft Cyst*

**A.** The wall of this empty cyst contains a dense lymphoid infiltrate. Lymphoid follicles containing germinal centers are present. **B.** This first branchial cleft remnant shows a keratin-filled cyst surrounded by eccrine and sebaceous glands. A nodule of hyaline cartilage is at the *top left*.



### Nodular Fasciitis

#### DEFINITION:

Nodular fibroblastic, myofibroblastic pseudosarcomatous proliferation showing a tissue culture–like appearance.

#### CLINICAL FEATURES:

- Wide age range, peak in decades 3 to 5 of life; M = F
- Soft tissues of neck, upper arm
- Rapid growing subcutaneous mass usually <1 month's duration, some painful

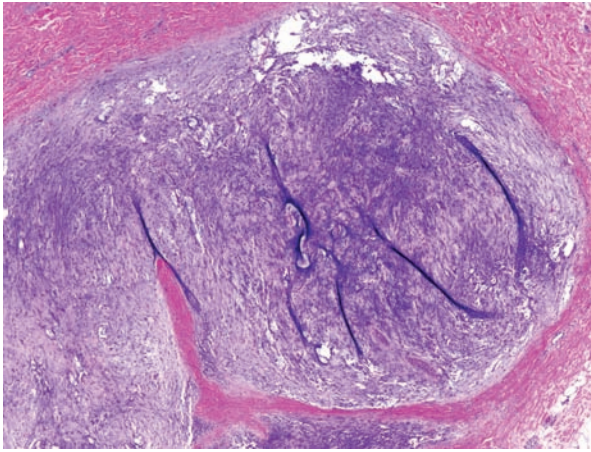
#### GROSS AND HISTOLOGIC FINDINGS:

- Gross: nodular nonencapsulated fibromyxoid nodule, <2 to 3 cm diameter
- Well-delimited nodule composed of uniform spindle cells in a focal storiform or tissue culture–like pattern with a stroma that varies from extremely myxoid to predominantly fibrous; spindle cell have oval-elliptical open nuclei with small nucleoli (**Figure 7-2**)
- Extravasation of red cells seen; mitoses common, never atypical
- Positive IHC: muscle specific actin, smooth muscle actin; negative for desmin, pan-cytokeratin, and CD34

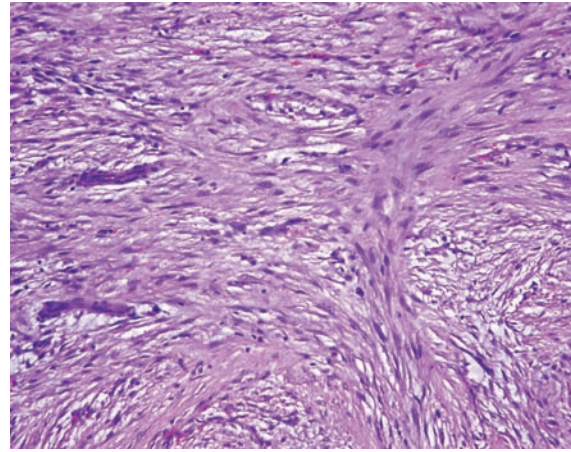
#### DIFFERENTIAL DIAGNOSIS:

- Dermatofibrosarcoma protuberans
- Dermatofibroma
- Fibromatosis

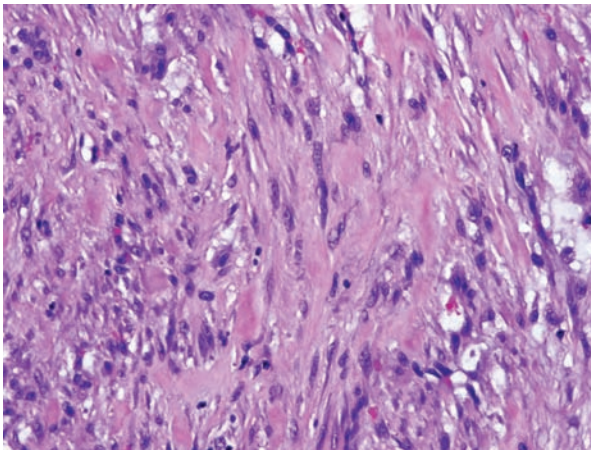
## Nodular Fasciitis



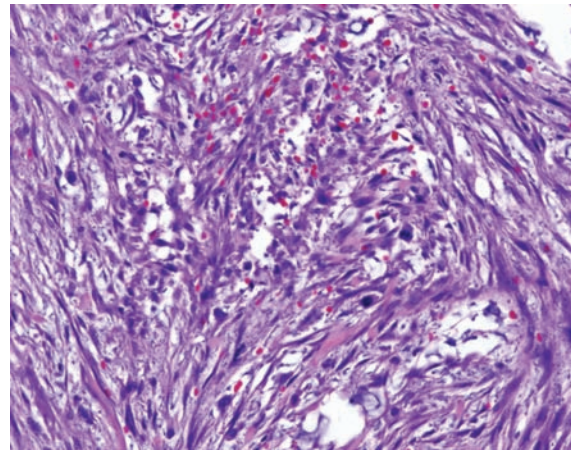
A



B



C



D

**FIGURE 7-2** *Nodular Fasciitis*

**A.** This dermal nodule has a smooth circumscribed contour. **B.** Myofibroblasts display a swirling, storiform pattern. **C.** This example shows a greater amount of keloidal-like collagen. Note the pale chromatin of spindle cells. **D.** Red cell extravasation is present in this example with more myxoid stroma.

### Lymphangioma

#### DEFINITION:

Benign neoplasm composed of lymphatic vessels.

#### CLINICAL FEATURES:

- Wide age range, mostly infants and children; no gender preference
- Oral cavity, soft tissue of neck, axilla

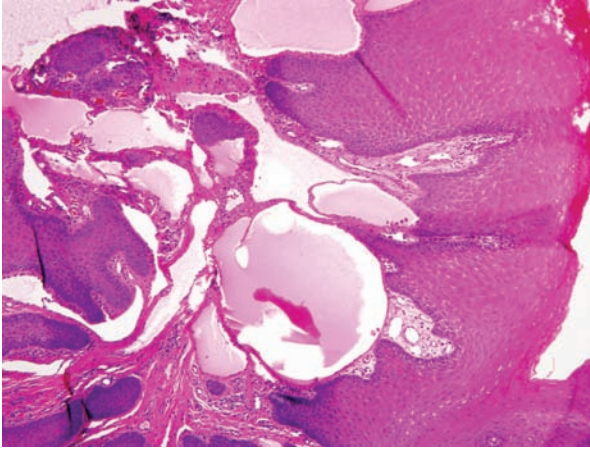
#### GROSS AND HISTOLOGIC FINDINGS:

- Gross: pink spongy tissue
- Anastomosing lymphatic channels lined by flattened cuboidal endothelial cells; typically dilated ectatic spaces containing amorphous eosinophilic lymph fluid with occasional red cells (**Figure 7-3**)
- Positive IHC: D2-40, CD31, Factor VIII-RAg, and CD34

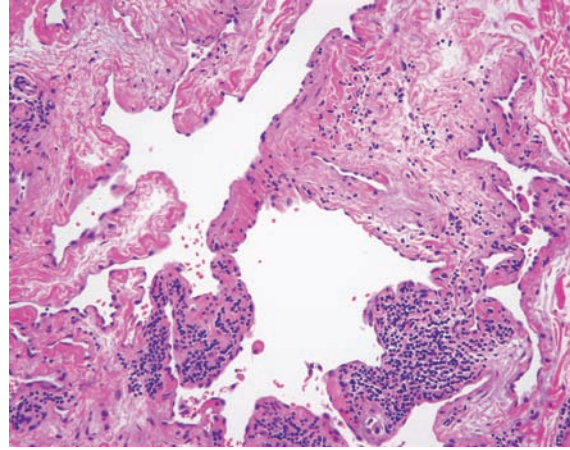
#### DIFFERENTIAL DIAGNOSIS:

- Hemangioma

## Lymphangioma



A



B

**FIGURE 7-3** *Lymphangioma*

**A.** Glossal lymphangioma with many small lymphatic spaces filled with eosinophilic lymph fluid and separated from each other by thin septa. **B.** Lymphangioma from the neck shows collapsed vascular slits with scattered lymphocytes.

### Teratoma

#### DEFINITION:

Neoplasm composed of tissues foreign to the site in which they arise. This section covers mature teratoma primarily.

#### CLINICAL FEATURES:

- Most common sites: nasopharynx, oropharynx, and soft tissues of neck
- Rare in adults; most children <1 year of age; no gender preference
- Painless mass; may cause respiratory distress in neonates

#### GROSS AND HISTOLOGIC FINDINGS:

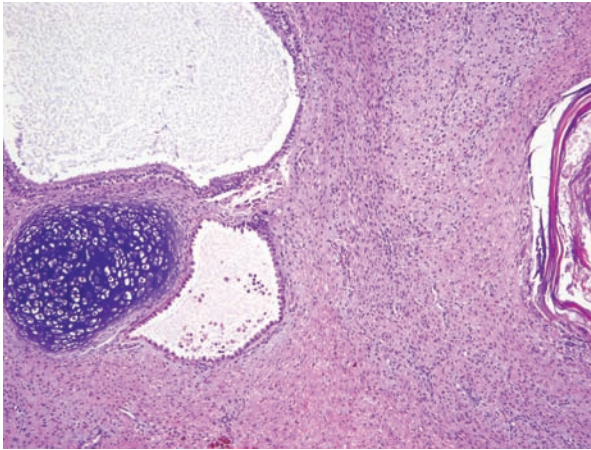
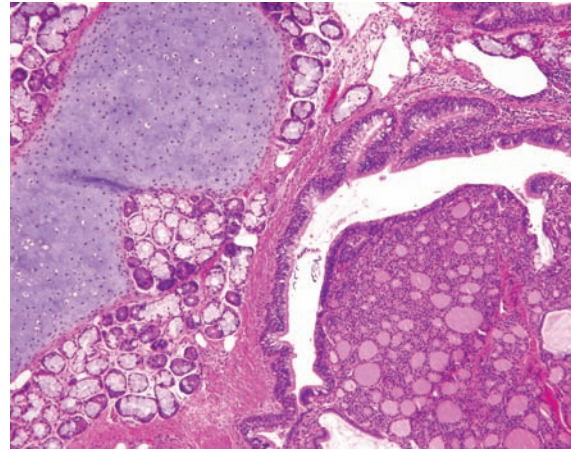
- Gross: variably cystic/solid with greasy sebum-like material, or strands of hair
- Haphazard mixture of keratinizing squamous, enteric, and respiratory epithelium, cutaneous adnexa, mature glial tissue, hyaline cartilage, skeletal muscle, fat, thyroid, and bone (**Figure 7-4**)
- Immature teratoma: presence of immature neuroepithelium
- Positive IHC: staining of epithelial tissue with pan-cytokeratins

#### DIFFERENTIAL DIAGNOSIS:

- Hamartoma
- Encephalocele (when only glial tissue is present)
- Malignant germ cell tumor arising in mature teratoma



## Teratoma

**A****B**

**FIGURE 7-4** *Teratoma*

**A.** Fibrous tissue contains a random mixture of cysts lined by respiratory epithelium adjacent to a nodule of cartilage, and a keratin-filled cyst (*right*). **B.** This mass includes pieces of histologically normal thyroid, minor salivary gland, cartilage, and respiratory mucosa.

### Fibromatosis

#### DEFINITION:

Benign proliferation of fibroblasts. Known as fibromatosis colli, or sternocleidomastoid tumor when localized to sternocleidomastoid muscle (SCM).

#### CLINICAL FEATURES:

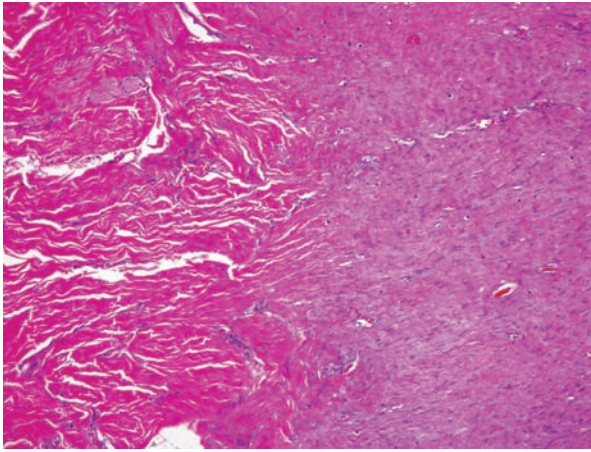
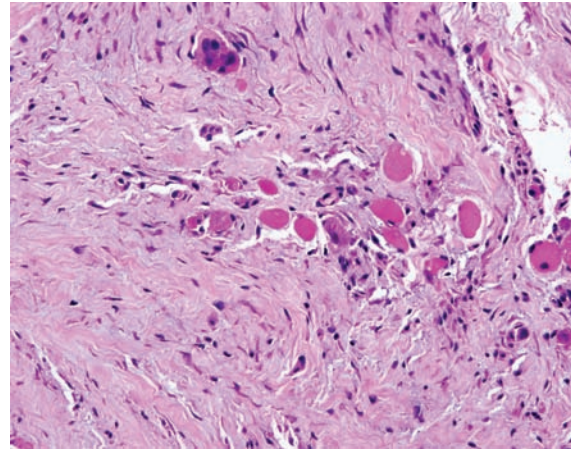
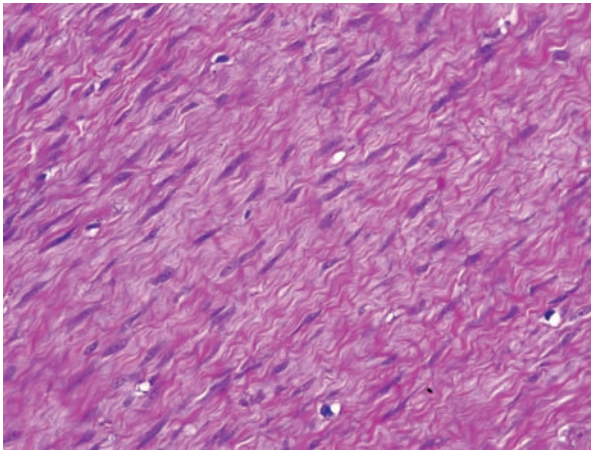
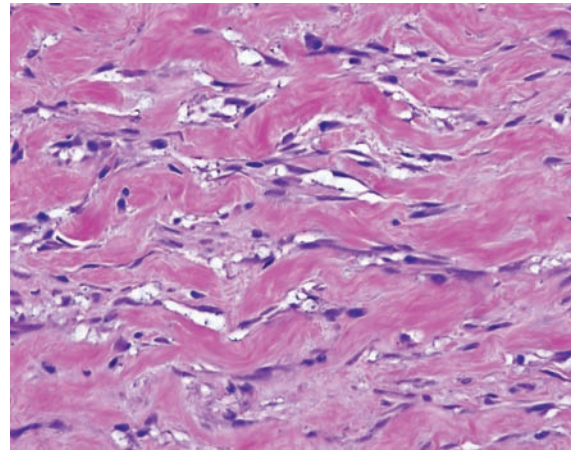
- Infants → older adults, peak in young adults; no gender preference
- Neck, sinonasal tract, oral cavity
- Firm rubbery mass, torticollis for SCM tumor

#### GROSS AND HISTOLOGIC FINDINGS:

- Gross: poorly delimited rubbery-firm nodule with a solid off-white cut surface
- Infiltrating variably cellular fibroblast proliferation in a variably dense collagenous stroma; uniform spindle shaped open nuclei with small distinctive nucleoli and bipolar cytoplasmic processes that merge with surrounding collagen (**Figure 7-5**)
- Jagged infiltration of skeletal muscle characterized by myofiber atrophy
- Positive IHC: vimentin,  $\beta$ -catenin, muscle specific actin, smooth muscle actin; S-100, CD34 negative

#### DIFFERENTIAL DIAGNOSIS:

- Fibrosarcoma
- Solitary fibrous tumor
- Schwannoma

**Fibromatosis****A****B****C****D**

**FIGURE 7-5** *Fibromatosis*

**A.** Fibromatosis (*right half*) imperceptibly infiltrates normal connective tissue. **B.** Fibromatosis colli with entrapment and atrophy of skeletal muscle at the tumor periphery. **C.** Parallel arrays of fibroblasts with hypochromic spindled nuclei and a ropy collagenous matrix. **D.** Collagen bands are much thicker in this example.

### Spindle Cell/Pleomorphic Lipoma

#### DEFINITION:

Benign lipomatous neoplasm characterized by the presence of a mixture of mature adipose tissue, bland spindle cells, multinucleated giant cells, and variable amount of collagen.

#### CLINICAL FEATURES:

- Young adults→ elderly with peak in decades 5 to 6; M:F = 8:1
- Painless nodule in subcutis of posterior neck, shoulder, and upper back

#### GROSS AND HISTOLOGIC FINDINGS:

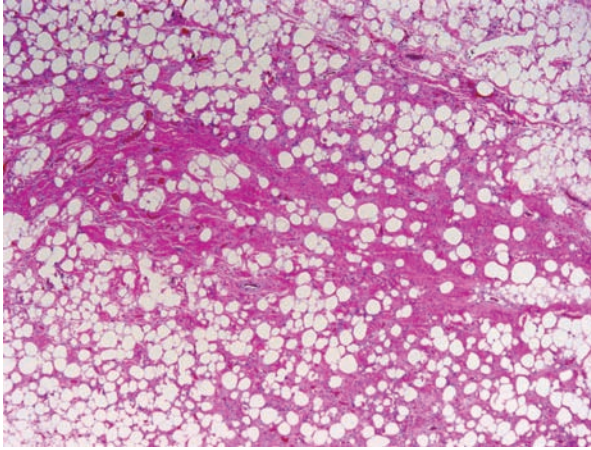
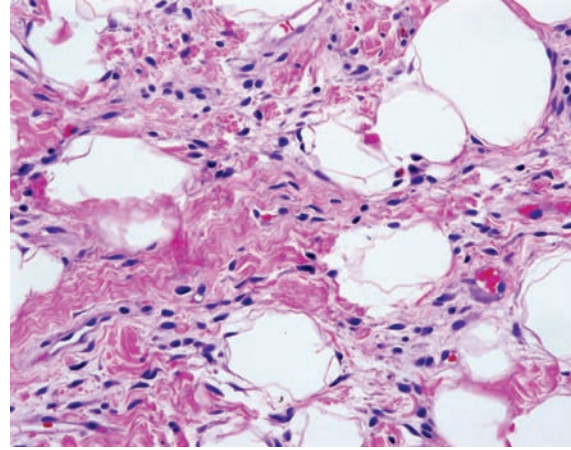
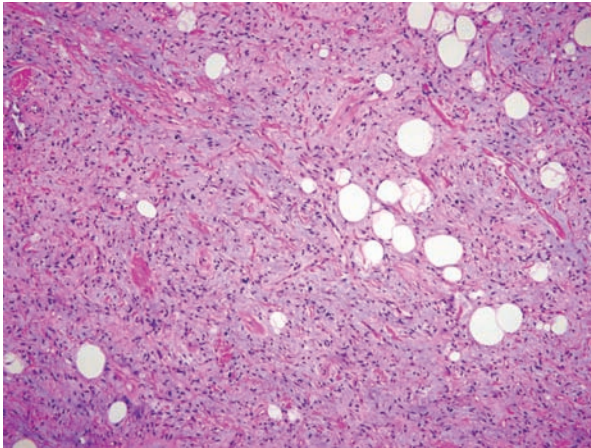
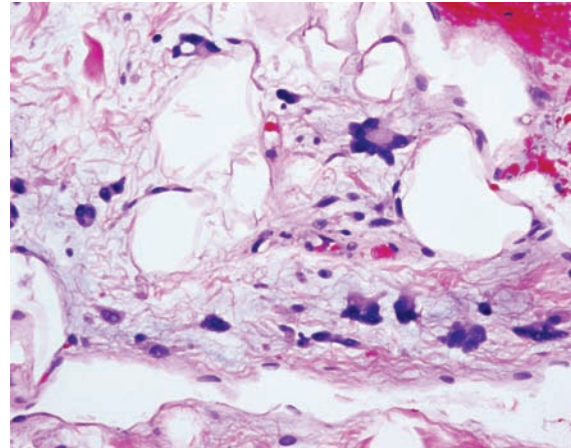
- Gross: bright yellow-gray white mass containing firm pink-white fibrous bands and variable myxoid change
- Mixed population of bland spindle cells, variable number of hyperchromatic multinucleated cells, mature adipose tissue, and collagen bands of variable thickness; multinucleated cell nuclei typically arranged in a ring or wreath-like pattern (**Figure 7-6**)
- May include myxoid stroma and slit-like spaces producing a pseudoangiomatous pattern; increased mast cells, rare mitoses
- Positive IHC: CD34, bcl-2, vimentin; negative staining with smooth muscle actin, desmin, S-100

#### DIFFERENTIAL DIAGNOSIS:

- Well-differentiated liposarcoma
- Dermatofibrosarcoma protuberans
- Nodular fasciitis
- Benign nerve sheath tumor



## Spindle Cell/Pleomorphic Lipoma

**A****B****C****D**

**FIGURE 7-6** *Spindle Cell/Pleomorphic Lipoma*

**A.** Small islands and streaks of fibrous tissue are embedded within fat.

**B.** Hyperchromatic spindle cells interdigitate among mature lipocytes and are associated with a variable amount of collagen. **C.** In contrast to image **A**, there is an abundance of fibromyxoid stroma and minimal adipose tissue. **D.** Focally numerous multinucleate cells; some display a peripheral radial (floret) arrangement.





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### **NONNEOPLASTIC LESIONS**

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# Index

NOTE: Locators followed by "f" indicate figures

ACC. *See* acinic cell adenocarcinoma (ACC)  
acinic cell adenocarcinoma (ACC), 104, 105f  
acoustic neuroma. *See* vestibular schwannoma  
AdCC. *See* adenoid cystic carcinoma (AdCC)  
adenoid cystic carcinoma (AdCC), 106, 107f  
AFC. *See* allergic fungal sinusitis (AFS)  
allergic fungal sinusitis (AFS), 32, 33f  
alveolar soft part sarcoma, 20, 21f  
ameloblastic fibroma, 128, 129f  
ameloblastoma, 126, 127f

basal cell adenoma, 96, 97f  
branchial cleft cyst, 166, 167f

calcifying epithelial odontogenic (Pindborg)  
tumor, 130, 131f  
carcinoma ex pleomorphic adenoma, 116, 117f  
cemento-ossifying fibroma. *See* ossifying  
fibroma  
ceruminous adenoma, 156, 157f  
cholesteatoma, 146, 147f  
cholesterol granuloma, 148, 149f  
chondrodermatitis nodularis chronicus helicis,  
144, 145f  
chronic fibrosing sialadenitis, 88, 89f  
chronic nonspecific sinusitis, 28, 29f  
clear cell carcinoma, NOS, 112, 113f  
contact ulcer, 58, 59f  
craniofacial osteosarcoma, conventional type,  
138, 139f

## ear

benign neoplasms  
ceruminous adenoma, 156, 157f  
endolymphatic sac papillary tumor, 162,  
163f  
jugulotympanic paraganglioma, 152, 153f  
langerhans cell histiocytosis, 150, 151f

middle ear adenoma, 158, 159f  
middle ear meningioma, 154, 155f  
vestibular schwannoma, 160, 161f  
nonneoplastic lesions  
cholesteatoma, 146, 147f  
cholesterol granuloma, 148, 149f  
chondrodermatitis nodularis chronicus  
helicis, 144, 145f  
keloid, 142, 143f  
endolymphatic sac papillary tumor, 162, 163f  
epithelial-myoepithelial carcinoma, 110, 111f  
epithelial precancerous lesions, 14, 15f, 70, 71f  
extranodal NK/T-cell lymphoma, nasal type,  
50, 51f

fibromatosis, 174, 175f  
fibrous dysplasia, craniofacial, 120, 121f  
fungal sinusitis, 34, 35f

glomangiopericytoma, 40, 41f  
gnathic bones

## benign neoplasms

ameloblastic fibroma, 128, 129f  
ameloblastoma, 126, 127f  
calcifying epithelial odontogenic  
(Pindborg) tumor, 130, 131f  
craniofacial osteosarcoma, conventional  
type, 138, 139f  
keratocystic odontogenic tumor,  
132, 133f  
odontogenic myxoma, 134, 135f  
odontoma, complex type, 136, 137f  
ossifying fibroma, 124, 125f  
osteoma/exostosis, 122, 123f  
nonneoplastic lesions  
fibrous dysplasia, craniofacial,  
120, 121f  
granular cell tumor, 10, 11f

- Heffner tumor. *See* endolymphatic sac  
papillary tumor  
hyperplastic alterations of mucosa, 64, 65f
- inflammatory myofibroblastic tumor, 68, 69f  
irritation fibroma, 6, 7f
- jugulotympanic paraganglioma, 152, 153f
- Kaposi sarcoma, 24, 25f  
keloid, 142, 143f  
keratocystic odontogenic tumor, 132, 133f  
Kuttner tumor. *See* chronic fibrosing  
sialadenitis
- Lane tumor. *See* spindle cell squamous  
carcinoma  
langerhans cell histiocytosis, 150, 151f  
laryngeal chondrosarcoma, 82, 83f  
laryngeal cysts, 62, 63f  
lobular capillary hemangioma, 38, 39f  
lymphangioma, 170, 171f  
lymphoepithelial sialadenitis, 90, 91f
- middle ear adenoma, 158, 159f  
middle ear meningioma, 154, 155f  
moderately differentiated neuroendocrine  
carcinoma, 80, 81f  
mucocele/ranula/mucus retention cyst, 4, 5f  
mucoepidermoid carcinoma, 102, 103f  
mucosal malignant melanoma, 52, 53f  
myoepithelioma, 100, 101f
- nasal cavity and paranasal sinuses  
benign neoplasms  
glomangiopericytoma, 40, 41f  
lobular capillary hemangioma,  
38, 39f  
Schneiderian papilloma, 36, 37f  
solitary fibrous tumor, 42, 43f  
malignant neoplasms  
extranodal NK/T-cell lymphoma, nasal  
type, 50, 51f  
mucosal malignant melanoma, 52, 53f  
olfactory neuroblastoma (ONB),  
46, 47f  
rhabdomyosarcoma (RMS), 54, 55f  
sinonasal adenocarcinoma (SNA),  
intestinal type, 44, 45f  
sinonasal undifferentiated carcinoma  
[SNUC], 48, 49f  
nonneoplastic lesions  
allergic fungal sinusitis (AFS),  
32, 33f  
chronic nonspecific sinusitis, 28, 29f  
fungal sinusitis, 34, 35f  
sinonasal polyps, 30, 31f  
nasopharyngeal angiofibroma, 12, 13f  
nasopharyngeal carcinoma, nonkeratinizing  
undifferentiated type, 18, 19f  
necrotizing sialometaplasia, 2, 3f  
nodular fasciitis, 168, 169f
- odontogenic keratocyst. *See* keratocystic  
odontogenic tumor  
odontogenic myxoma, 134, 135f  
odontoma, complex type, 136, 137f  
olfactory neuroblastoma (ONB), 46, 47f  
ONB. *See* olfactory neuroblastoma (ONB)  
oncocyoma, 98, 99f  
oral cavity/nasopharynx  
benign neoplasms  
epithelial precancerous lesions,  
14, 15f  
granular cell tumor, 10, 11f  
nasopharyngeal angiofibroma, 12, 13f  
rhabdomyoma, adult type, 8, 9f  
malignant neoplasms  
alveolar soft part sarcoma, 20, 21f  
epithelial precancerous lesions, 14, 15f  
Kaposi sarcoma, 24, 25f  
nasopharyngeal carcinoma,  
nonkeratinizing undifferentiated type,  
18, 19f  
plasmablastic lymphoma, 22, 23f  
squamous cell carcinoma, conventional  
type, 16, 17f  
nonneoplastic lesions  
irritation fibroma, 6, 7f  
mucocele/ranula/mucus retention cyst,  
4, 5f  
necrotizing sialometaplasia, 2, 3f  
oro/hypopharynx/larynx  
benign neoplasms  
inflammatory myofibroblastic tumor,  
68, 69f  
squamous papilloma, 66, 67f



- 
- malignant neoplasms
    - epithelial precancerous lesions, 70, 71f
    - laryngeal chondrosarcoma, 82, 83f
    - moderately differentiated
      - neuroendocrine carcinoma, 80, 81f
    - papillary squamous cell carcinoma, 76, 77f
    - small cell neuroendocrine carcinoma, 78, 79f
    - spindle cell squamous carcinoma, 74, 75f
    - verrucous carcinoma, 72, 73f
  - nonneoplastic lesions
    - contact ulcer, 58, 59f
    - hyperplastic alterations of mucosa, 64, 65f
    - laryngeal cysts, 62, 63f
    - vocal cord polyp/nodules, 60, 61f
  - ossifying fibroma, 124, 125f
  - osteoma/exostosis, 122, 123f
  
  - papillary squamous cell carcinoma, 76, 77f
  - plasmablastic lymphoma, 22, 23f
  - pleomorphic adenoma, 92, 93f
  - polymorphous low-grade adenocarcinoma, 108, 109f
  - pyogenic granuloma. *See* lobular capillary hemangioma
  
  - rhabdomyoma, adult type, 8, 9f
  - rhabdomyosarcoma (RMS), 54, 55f
  
  - salivary duct carcinoma, 114, 115f
  - salivary gland
    - benign neoplasms
      - basal cell adenoma, 96, 97f
      - myoepithelioma, 100, 101f
      - oncocytoma, 98, 99f
      - pleomorphic adenoma, 92, 93f
      - Warthin tumor, 94, 95f
    - malignant neoplasms
      - acinic cell adenocarcinoma (ACC), 104, 105f
      - adenoid cystic carcinoma (AdCC), 106, 107f
      - carcinoma ex pleomorphic adenoma, 116, 117f
      - clear cell carcinoma, NOS, 112, 113f
      - epithelial-myoepithelial carcinoma, 110, 111f
      - mucoepidermoid carcinoma, 102, 103f
      - polymorphous low-grade adenocarcinoma, 108, 109f
      - salivary duct carcinoma, 114, 115f
    - nonneoplastic lesions
      - chronic fibrosing sialadenitis, 88, 89f
      - lymphoepithelial sialadenitis, 90, 91f
      - sialolithiasis, 86, 87f
  - Schneiderian papilloma, 36, 37f
  - schwannoma. *See* vestibular schwannoma
  - sialolithiasis, 86, 87f
  - sinonasal adenocarcinoma (SNA), intestinal type, 44, 45f
  - sinonasal polyps, 30, 31f
  - sinonasal undifferentiated carcinoma (SNUC), 48, 49f
  - small cell neuroendocrine carcinoma, 78, 79f
  - SNA. *See* sinonasal adenocarcinoma (SNA), intestinal type
  - SNUC. *See* sinonasal undifferentiated carcinoma (SNUC)
  - soft tissues
    - benign neoplasms
      - fibromatosis, 174, 175f
      - lymphangioma, 170, 171f
      - spindle cell/pleomorphic lipoma, 176, 177f
      - teratoma, 172, 173f
    - nonneoplastic lesions
      - branchial cleft cyst, 166, 167f
      - nodular fasciitis, 168, 169f
  - solitary fibrous tumor, 42, 43f
  - spindle cell/pleomorphic lipoma, 176, 177f
  - spindle cell squamous carcinoma, 74, 75f
  - squamous cell carcinoma, conventional type, 16, 17f
  - squamous papilloma, 66, 67f
  
  - teratoma, 172, 173f
  
  - verrucous carcinoma, 72, 73f
  - vestibular schwannoma, 160, 161f
  - vocal cord polyp/nodules, 60, 61f
  
  - Warthin tumor, 94, 95f
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